School of Physiotherapy and Exercise Science

Surgical Resection for Lung Cancer: Optimising Patient Evaluation and Recovery

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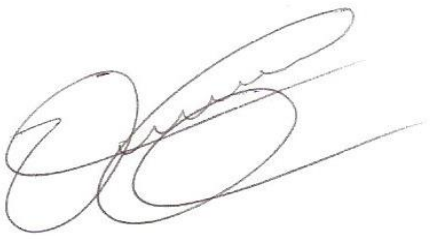
This thesis is presented for the Degree of
Doctor of Philosophy
of
Curtin University

September 2014

DECLARATION

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature: 

Date: 03/09/2014

STATEMENT OF ORIGINALITY

This thesis is presented for the degree of Doctor of Philosophy at Curtin University Western Australia. Studies were undertaken between March 2011 and August 2014, through the School of Physiotherapy and Exercise Science at Curtin University, in association with the Department of Pulmonary Physiology and the Physiotherapy Department at Sir Charles Gairdner Hospital and the Department of Respiratory Medicine and Physiotherapy Department at Royal Perth Hospital.

This research project was developed in association with my supervisors who have been involved in editing both this thesis and all associated publications. All material presented in this thesis is original.

ABSTRACT

Background and research questions

This programme of research was designed to: (i) evaluate the current evidence for exercise training in people following lung resection for non-small cell lung cancer (NSCLC) and; (ii) examine current physiotherapy practice patterns for people undergoing lung resection for lung cancer in Australia and New Zealand. Further, in people following curative intent treatment (i.e. lobectomy with or without adjuvant chemotherapy) for stage I, II or IIIA NSCLC, this programme of research was designed to: (iii) evaluate the magnitude of impairments in functional outcomes; (iv) investigate patterns of sedentary behaviour and physical activity; (v) compare peak exercise responses as well as patterns of change in exercise responses during the six-minute walk test (6MWT) and the cardiopulmonary exercise test (CPET) and; (vi) investigate the effects of supervised exercise training on recovery of functional outcomes. The studies were designed to address the following research questions:

1. What is the current evidence for exercise training in people following lung resection for NSCLC?

2. What are the current physiotherapy practice patterns for people undergoing lung resection for lung cancer in Australia and New Zealand?

3. Compared with age and gender-matched healthy controls, are measures of exercise capacity, health related quality of life (HRQoL), peripheral muscle force, physical activity, lung function and feelings of anxiety and depression impaired in people following curative intent treatment for NSCLC?

4. Do patterns of sedentary behaviour and physical activity of people following curative intent treatment for NSCLC differ from those in age and gender-matched healthy controls?

5. Does the 6MWT elicit similar peak exercise responses and patterns of change in heart rate (HR) and arterial oxygen saturation measured via pulse oximetry (SpO_2) as the CPET in people following curative intent treatment for NSCLC?

6. What are the effects of supervised exercise training on exercise capacity, HRQoL, peripheral muscle force, physical activity and sedentary behaviour, lung function, functional limitation resulting from dyspnoea and fatigue, and feelings of anxiety and depression in people following curative intent treatment for NSCLC?

Study 1: Current evidence for exercise training in people following lung resection for NSCLC: Cochrane systematic review

Background: Decreased exercise capacity and impairments in HRQoL are common in people following lung resection for NSCLC. Exercise training has been demonstrated to result in gains in exercise capacity and HRQoL for people with a range of chronic conditions, including chronic obstructive pulmonary disease (COPD) and heart failure, as well as in people with other cancers, such as prostate and breast cancer. A programme of exercise training may also result in important gains in these outcomes for people following lung resection for NSCLC. To date, evidence of the efficacy of a programme of exercise training for people following lung resection for NSCLC is unclear. The aim of this systematic review was to assess the effects of exercise training on exercise capacity, HRQoL, lung function (forced expiratory volume in one second [FEV_1]) and quadriceps force in people who have had a recent lung resection for NSCLC.

Methods: This Cochrane systematic review comprised three randomised controlled trials (RCTs) of exercise training following lung resection for NSCLC. The three RCTs included a total of 178 participants. Meta-analyses were performed for outcomes of exercise capacity, HRQoL and lung function.

Results: For people who required lung resection for NSCLC, exercise training conferred an improvement in six-minute walk distance (6MWD) (mean difference (MD) [95% confidence interval (CI)]: 50 [15 to 85] m). On completion of the intervention period, there was no difference in HRQoL (standardised MD [95% CI]: 0.17 [-0.16 to 0.49]) or FEV_1 (MD [95% CI]: -0.13 [-0.36 to 0.11] L) between intervention and control groups. Between-group differences in quadriceps force were not found. The quality of the evidence of the studies included in the analyses was poor.

Discussion and conclusions: The meta-analyses demonstrated that exercise training increased exercise capacity, measured as 6MWD, in people following lung resection for NSCLC. An increase in 6MWD following exercise training is an important finding because this measure appears to be a valuable prognostic indicator for people with NSCLC. The review suggests that exercise training has little effect on HRQoL for people following lung resection for NSCLC. However, two included studies did not use disease-specific HRQoL questionnaires, which are likely to be more responsive to changes in this outcome compared with generic HRQoL questionnaires. Therefore, larger RCTs using disease-specific HRQoL questionnaires are needed to further investigate the effects of exercise training on HRQoL in people following lung resection for NSCLC. Changes in lung function following exercise training were not demonstrated in this review and this is in agreement with the literature pertaining to effect of exercise training on lung function for people with COPD. There was insufficient data to comment on the effect of exercise training on quadriceps force.

Study 2: Physiotherapy practice patterns for people undergoing lung resection: Survey

Background: There has been a recent increase in the research available to guide physiotherapy management of patients who require surgical resection for lung cancer. However, it is unclear whether this evidence has influenced clinical practice. The aim of this survey was to describe physiotherapy practice patterns in the pre- and post-operative management of patients who undergo surgical resection for lung cancer.

Methods: A questionnaire was developed for use in this study and was piloted by four experienced physiotherapists in order to optimise its face validity, readability and structure. The questionnaire was posted to senior cardiothoracic physiotherapists of 49 hospitals in Australia and New Zealand (43 hospitals in Australia and six in New Zealand). The Tailored Design Method (Dillman approach) was used to optimise response rate.

Results: Staff in two of the 49 hospitals declined participation. Of the 47 sites that consented to participate, 43 (91%) completed and returned the questionnaire. Prior to

surgery, patients in the majority of hospitals were assessed by a physiotherapist (n = 26; 60%), but did not participate in supervised exercise training (n = 39; 91%). Following surgery, physiotherapy was commenced on the first post-operative day (n = 39; 91%), with walking-based exercise being the most frequent treatment undertaken (n = 40; 93%). Seventy-two per cent of respondents referred less than 25% of their patients to exercise training on discharge from hospital. Physiotherapy practice was influenced predominantly by established practice in the hospital and personal experience and not by research findings.

Discussion and conclusions: The survey demonstrated that physiotherapy services for patients with lung cancer undergoing surgical resection throughout Australia and New Zealand currently focus on minimising the immediate risk of post-operative pulmonary complications. Although physiotherapy was most often commenced on the day following surgery, with walking-based exercise being the most frequently implemented treatment, referral to exercise training programmes was uncommon for this patient population. This might have been due to a scarcity of well-designed studies, published prior to undertaking this survey, which demonstrated the benefits of exercise training for this patient population. The response rate was 91% and therefore the results of the survey provide a representative snapshot of current physiotherapy practice patterns for patients undergoing surgery for lung cancer across Australia and New Zealand.

Study 3: Impairments in people following lobectomy for NSCLC compared to healthy controls

Background: Earlier studies have reported decrements in lung function, maximal exercise capacity and HRQoL in people following curative intent treatment for NSCLC. However, the magnitude of these impairments compared to healthy people remains unknown. Further, it is also unknown whether people following curative intent treatment for NSCLC present impairments in other measures that are likely to be important, such as 6MWD, peripheral muscle force, physical activity, and feelings of anxiety and depression. The aim of this study was to compare measures of exercise capacity, HRQoL, peripheral muscle force, physical activity, lung function

and feelings of anxiety and depression in people following curative intent treatment for NSCLC with age and gender-matched healthy controls.

Methods: This cross-sectional study included 23 people (68 ± 10 yr; 16 females) 6 to 10 weeks after lobectomy for NSCLC or, for those who went onto receive adjuvant chemotherapy, 4 to 8 weeks after their last cycle of chemotherapy (the NSCLC group). The study also included 20 age and gender-matched healthy controls (69 ± 5 yr; 13 females). Participants underwent measurements of exercise capacity (CPET and 6MWT), HRQoL (the medical outcomes study short form 36 general health survey [SF-36]), physical activity (7 consecutive days wearing both the SenseWear armband [SWA] and the Stepwatch activity monitor [SAM] during waking hours), peripheral muscle force (isometric quadriceps torque and handgrip force), lung function (spirometry) and feelings of anxiety and depression (the hospital anxiety and depression scale [HADS]). Between-group comparisons of continuous data were undertaken using independent-samples *t*-test. Pearson Chi-square was used for comparison of categorical data. For measures of functional outcomes that differed between the NSCLC group and healthy controls, data from the healthy controls were used to calculate the lower limit of normal (LLN).

Results: Regarding exercise capacity, when compared with data collected in healthy controls, the peak rate of oxygen consumption (VO_{2peak}), maximum work rate (Wmax) and 6MWD of people in the NSCLC group (15 ± 3 $ml \cdot kg^{-1} \cdot min^{-1}$, 75 ± 25 W and 494 ± 77 m, respectively) were decreased by 38%, 39% and 24% ($p < 0.001$ for all), respectively. Seventy-one per cent of people in the NSCLC group had a VO_{2peak} below the LLN. Lower scores for the two summary components and all eight domains of the SF-36 were demonstrated in the NSCLC group. The isometric handgrip force of participants in the NSCLC group was lower than that in healthy controls (28 ± 7 *versus* 34 ± 10 kg; $p = 0.02$). Daily step count measured by the SAM was also lower in the NSCLC group (8,863 ± 3,737 steps/day) compared with healthy controls (11,856 ± 3,024 steps/day) ($p = 0.009$). Following curative intent treatment for NSCLC, isometric quadriceps torque, time spent in moderate-to-vigorous physical activity and feelings of anxiety and depression were similar to that measured in age and gender-matched healthy controls.

Discussion and conclusions: Of the outcomes measured, the greatest impairment detected in people following curative intent treatment for NSCLC, compared to healthy controls, was in exercise capacity. Compared to age and gender-matched healthy controls, people following curative intent treatment for NSCLC also demonstrated impairments in HRQoL, isometric handgrip force, lung function and daily step count. These findings provide important information for clinicians working with this population. They highlight the need to refer people following curative intent treatment for NSCLC to exercise training programmes. As reported in the Cochrane systematic review, exercise capacity can be improved with exercise training. However, as demonstrated in the survey, referral to exercise training following lung resection for lung cancer is uncommon.

Study 4: Patterns of sedentary behaviour and physical activity in people following lobectomy for NSCLC compared to healthy controls

Background: In both healthy people and patient populations, increased interest has emerged on the role of sedentary behaviour and physical activity on health outcomes and on the risk of developing chronic diseases. Although there has been some research investigating the way in which time in sedentary behaviour and physical activity are accumulated in healthy individuals, people following bariatric surgery, people with moderate to severe COPD and females with breast cancer, there is no information on patterns of sedentary behaviour and physical activity in people following curative intent treatment for NSCLC. The aim of this study was to compare patterns of sedentary behaviour and physical activity in people following curative intent treatment for NSCLC with age and gender-matched healthy controls

Methods: A sub-analysis of data collected during the cross-sectional study (Study 3) was undertaken. Sedentary behaviour and physical activity data were available for 20 participants following curative intent treatment for NSCLC (68 ± 10 yr; 13 females) and 20 age and gender-matched healthy controls (69 ± 5 yr; 13 females). Utilising SWA data, metabolic equivalent units (METs) were used to classify the proportion of time during waking hours participants spent in sedentary behaviour (<1.5 METs),

light intensity (1.5 to <3.0 METs) and moderate-to-vigorous intensity physical activity (≥3.0 METs). Daily step count was measured via the SAM.

Results: Compared with the healthy controls, people following curative intent treatment for NSCLC spent a lower percentage of their waking hours in light intensity physical activity (26.4 ± 7.8 *versus* 20.7 ± 9.0% of waking hours; p = 0.04). The percentage of time in sedentary behaviour accumulated in uninterrupted bouts ≥ 30 minutes was 7% greater in the NSCLC group compared to healthy controls (p = 0.048). The percentage of waking hours spent in moderate-to-vigorous intensity physical activity was similar between the groups (11.3 ± 10.1% of waking hours [NSCLC group] *versus* 11.6 ± 10.7% of waking hours [healthy controls]; p = 0.92). As reported in Study 3, daily step count was lower in the NSCLC group (8,863 ± 3,737 steps/day) compared with healthy controls (11,856 ± 3,024 steps/day) (p = 0.009).

Discussion and conclusions: Although participants in the NSCLC group spent a similar proportion of time in moderate-to-vigorous intensity physical activity, they spent less time than healthy controls performing light intensity physical activity and more time in prolonged uninterrupted bouts of sedentary behaviour. Prolonged time in sedentary behaviour has been related to an increase in waist circumference, higher concentration of triglycerides as well as a clustered metabolic risk score in the general population, being a potential risk factor for metabolic diseases. Of note, an almost perfect inverse relationship between time spent in light intensity physical activity and time spent in sedentary behaviour has been reported. Therefore, strategies aiming at displacing time in sedentary behaviour with time in light intensity physical activity may improve health outcomes in people following curative intent treatment for NSCLC and warrants further investigation.

Study 5: Comparison between peak and patterns of exercise responses following lobectomy for NSCLC during two exercise tests

Background: The CPET is accepted as the gold standard method to quantify exercise capacity, evaluate exercise limitation and prescribe cycling training. In people following curative intent treatment for NSCLC, the 6MWT has been used to prescribe the intensity for a walking training programme and to evaluate changes in

exercise capacity following training. However, no study has compared the physiological and symptom responses elicited during the 6MWT to those elicited during the CPET in this population. The aim of this study was to compare peak exercise responses and patterns of change in HR and SpO_2 during the 6MWT and the CPET.

Methods: A sub-analysis of data collected during the cross-sectional study (Study 3) was undertaken. Complete 6MWT and CPET data were available in 20 participants following curative intent treatment for NSCLC (67 ± 10 yr; 14 females). Peak exercise responses, symptoms of dyspnoea and fatigue (BORG scale 0-10) as well as patterns of change in HR and SpO_2 during the 6MWT were compared to those during the CPET.

Results: The 6MWT elicited a somewhat lower peak HR than the CPET (119 ± 15 *versus* 128 ± 18 bpm; $p = 0.02$). However there was no difference in the magnitude of change from resting to peak HR (ΔHR) between the CPET and 6MWT (MD [95% CI]; 7 [-15 to 1] bpm; $p = 0.10$). In contrast, the magnitude of decrement in SpO_2 was greater during the 6MWT than during the CPET (MD [95% CI]; -2 [-4 to -1]%; $p < 0.01$). People following curative intent treatment for NSCLC reported less dyspnoea and leg fatigue on completion of 6MWT compared to the CPET (MD [95% CI]; -3.8 [-5.0 to -2.6] and -4.8 [-6.2 to -3.4], respectively; $p < 0.001$ for both). Regarding the pattern of response, a plateau in the HR and SpO_2 responses occurred after the end of the third and second minute of the 6MWT, respectively, whereas during the CPET, there was a linear increase in HR and decrease in SpO_2 with increasing work rate.

Discussion and conclusions: This study suggests that the 6MWT elicited a somewhat lower peak HR than the CPET. However, the ΔHR during the 6MWT was comparable to that during the CPET. Further, the 6MWT was more sensitive than the CPET at detecting oxygen desaturation in people following curative intent treatment for NSCLC. Participants following curative intent treatment for NSCLC reported less dyspnoea and leg fatigue at the end of the 6MWT than at the end of the CPET. In contrast with the CPET, plateaus were observed in HR and SpO_2 responses during the 6MWT. These results suggest that the 6MWT should be considered a

complementary test to the CPET and may be useful when prescribing walking training in people following curative intent treatment for NSCLC.

Study 6: Effects of exercise training following lobectomy for NSCLC: RCT

Background: The role of exercise training is well established in many chronic respiratory conditions. Exercise training also plays an important role for individuals with a variety of cancer diagnoses such as breast and prostate cancer. Data from single group studies in people following curative intent treatment for NSCLC suggest that exercise training is feasible and safe and may confer benefits in dyspnoea, exercise capacity and HRQoL. Conclusions from RCTs of exercise training in this population are limited due to some methodological limitations such as providing a home-based exercise training programme, only including participants who underwent open thoracotomy, lacking blinding of the outcome assessor and using generic or non-disease-specific questionnaires to assess HRQoL. The aim of this RCT was to investigate the effects of supervised exercise training on exercise capacity, HRQoL, peripheral muscle force, physical activity and sedentary behaviour, lung function, functional limitation resulting from dyspnoea and fatigue, and feelings of anxiety and depression in people following curative intent treatment for NSCLC.

Methods: The RCT of exercise training following lobectomy for NSCLC included 17 participants (67 ± 9 yr; FEV_1 66 ± 17%pred; 12 females) who participated in the cross-sectional study (Study 3). Baseline assessments were 6 to 10 weeks after lobectomy for NSCLC or, for those who went onto receive adjuvant chemotherapy, 4 to 8 weeks after their last cycle of chemotherapy. People were randomised to either 8 weeks of exercise training (exercise training group) or 8 weeks of usual care (control group). Prior to and immediately following the 8 weeks of intervention, both groups underwent measurements of exercise capacity (CPET and 6MWT), HRQoL (SF-36, the functional assessment of cancer therapy – lung scale [FACT-L] and the European organisation for research and treatment of cancer, quality of life questionnaire core 30 [EORTC QLQ-C30]), physical activity (7 consecutive days wearing both the SWA and the SAM during waking hours), peripheral muscle force (isometric quadriceps torque and handgrip force), lung function (spirometry, body

plethysmography and diffusing capacity for carbon monoxide), functional limitation resulting from dyspnoea (the modified medical research council dyspnoea scale [MMRC]), fatigue (the functional assessment of chronic illness therapy - fatigue subscale [FACIT-Fatigue]) and feelings of anxiety and depression (HADS). Participants in the exercise training group who attended at least 60% of exercise training sessions over the 8-week training period (i.e. 15 of 24 sessions) were classified as "adherent" with exercise training.

Results: Of the 17 participants who completed the baseline assessments, nine were randomised to the exercise training group (66 ± 10 yr; FEV_1 61 ± 17%pred; six females) and eight were randomised to the control group (68 ± 9 yr; FEV_1 71 ± 15%pred; six females). Of the nine participants who were randomised to the exercise training group, four completed at least 15 sessions (i.e. 60% of the total number of sessions) and were deemed to be adherent with exercise training. In people following curative intent treatment for NSCLC, exercise training resulted in improvements in exercise capacity. Following the intervention period, the intention-to-treat (ITT) analysis without data imputation showed that the increase in VO_{2peak} ($L \cdot min^{-1}$), VO_{2peak} (%pred), O_2 pulse, anaerobic threshold as a percentage of the VO_{2peak} (AT) and 6MWD in the exercise training group was greater than any change in the control group (MD [95% CI] 0.19 [0.04 to 0.33] $L \cdot min^{-1}$; 10 [2 to 19]%pred; 2 [0 to 3] $ml \cdot beat^{-1}$; 11 [1 to 21]%; 52 [12 to 93] m; $p < 0.05$ for all). The ITT analysis using the baseline-carried-forward method showed similar results, demonstrating that the increase in VO_{2peak} ($L \cdot min^{-1}$), VO_{2peak} (%pred), O_2 pulse and 6MWD in the exercise training group was greater than any change in the control group (MD [95% CI] 0.14 [0.01 to 0.27] $L \cdot min^{-1}$; 8 [1 to 15]%pred; 1 [0 to 2] $ml \cdot beat^{-1}$; 36 [3 to 70] m; $p < 0.05$ for all). No between-group differences in other outcome measures were observed.

Discussion and conclusions: This study demonstrated that an 8-week supervised exercise training programme resulted in improvements in maximal exercise capacity and 6MWD in people following curative intent treatment for NSCLC. No changes in other outcome measures were observed. These findings support the findings from the Cochrane systematic review. Further, they provide novel information showing that measures of maximal exercise capacity, such as VO_{2peak}, O_2 pulse and AT also

improve following exercise training in this population. The current RCT addressed the limitations of previous RCTs by providing a supervised exercise training programme, including both people who underwent open thoracotomy and people who underwent video-assisted thoracoscopic surgery, blinding the outcome assessor and using both disease-specific and generic questionnaires to assess HRQoL. Taken together with the results of the cross-sectional study, that demonstrated substantial impairments in exercise capacity relative to healthy controls, the findings of the current study highlight the need to refer people following curative intent treatment for NSCLC to exercise training programmes.

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ACKOWLEDGEMENTS AND FUNDING

Curtin University (Curtin Strategic International Research Scholarship [CSIRS]), Sir Charles Gairdner Hospital (SCGH - Research Advisory Committee Grant [number 2011/12/013]) and Lung Institute of Western Australia (PhD Top-up Scholarship Award) for supporting this programme of research.

Associate Professors Kylie Hill and Sue Jenkins, my PhD supervisors, for their invaluable guidance, expertise, commitment, patience and support. For humbly assisting me with recruitment, contacting and training participants and engaging in all aspects of each study in this research programme. You are both "Giants", and it was a pleasure for me to see further and contemplate the beauty of science by standing on your shoulders.

Nola Cecins for her support and assistance with training the participants of the randomised controlled trial as well as for the feedback provided on conference abstracts, papers and conference presentations.

Carol Watson for opening doors for recruitment, assessment and training of participants at Royal Perth Hospital. Also, for the instructions in the use of the equipment to assess quadriceps torque and familiarisation with the protocol.

Kirsten Mooney for her kindness and dedication during the recruitment stage of the studies. Her assistance was indispensable to the completion of this programme of research.

Dr Kevin Gain for all he has taught me. For constantly making me think beyond the walls of my knowledge. I will never forget his words: "*Life gets boring when things cannot be improved*". I am also appreciative of the many hours of lung function and exercise capacity testing.

Michelle Melang for the dedication when training and following up participants.

Dr Martin Phillips, Dr Lucas Sanders, Dr Jeanie Leong, Prof Mark Edwards and Dr Pragnesh Joshi for being supportive with the studies right from the beginning.

Dr John McLachlan for hours of exercise test supervision.

Bill Noffsinger for his advice and help when I had issues with the maximal exercise capacity equipment.

Mika Nonoyama for the assistance with the Cochrane systematic review.

Cindy Ng for the guidance throughout the initial steps of my new life in Perth as well as during the initial stages of this programme of research.

Ben Noteboom for the assistance when recruiting healthy controls.

The Physiotherapy Department at Sir Charles Gairdner Hospital (SCGH) and Royal Perth Hospital (RPH) for the friendly staff. I am also grateful for the office space provided and use of resources during the recruitment and data collection phases.

All the staff from the Pulmonary Physiology Department at SCGH and from the Respiratory Medicine Department at RPH for their assistance with lung function and exercise tests and their continued friendship and support.

The Senior Physiotherapists who participated in the survey for their time in completing the questionnaire and their promptness in mailing it back.

All the participants of the studies for their time, patience and effort.

Beatriz, Juliana, Joel, Mohammed, Fatim and other colleagues from the HUB of HDR students for sharing experiences and for their constant support.

My friends Andresa, Rodrigo, Guilherme and Juliana for assisting me with proof reading chapters of this thesis.

My family back home (Edevaldo [Dad], Lucia [Mum] and Henrique [Brother]) for being supportive; for their love and encouragement.

My brave wife, Fernanda, who embraced the challenge of moving to Perth and faced all the obstacles with grace, courage and faith. You are a champion. Thank you for always being by my side.

Above all, God, who is my source of inspiration and happiness; my strength, shield and shelter.

PUBLICATIONS ARISING FROM THIS THESIS

Peer reviewed journals

Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K.. Exercise training undertaken within 12 months following lung resection for patients with non-small cell lung cancer (Protocol). *Cochrane Database of Systematic Reviews.* 2012, Issue 7, Art No.: CD009955. DOI: 10.1002/14651858.CD009955.

Cavalheri V, Jenkins S, Hill K. Physiotherapy practice patterns for patients undergoing surgery for lung cancer: A survey of hospitals in Australia and New Zealand. *Internal Medicine Journal.* 2013 Apr; 43(4):394-401.

Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K.. Exercise training undertaken by people within 12 months following lung resection for non-small cell lung cancer. *Cochrane Database of Systematic Reviews.* 2013, Issue 7, Art No.: CD009955. DOI: 10.1002/14651858.CD009955.pub2.

Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K.. Exercise training for people following lung resection for non-small cell lung cancer – A Cochrane systematic review. *Cancer Treatment Reviews.* 2014; 40(4): 585-94.

Manuscripts in preparation

Cavalheri V, Jenkins S, Cecins N, Hill K. Outcomes following curative intent treatment for non-small cell lung cancer: A comparison with age and gender matched healthy controls

Cavalheri V, Jenkins S, Gain K, Cecins N, Hill K. Exercise responses during the cardiopulmonary exercise test and the six-minute walk test following curative intent treatment for non-small cell lung cancer

Cavalheri V, Jenkins S, Cecins N, Hill K. Patterns of sedentary behaviour and physical activity following curative intent treatment for non-small cell lung cancer

Cavalheri V, Jenkins S, Gain K, Cecins N, Hill K. Exercise training for people following curative intent treatment for non-small cell lung cancer: A randomised controlled trial

Abstracts

Cavalheri V, Jenkins S, Hill K. Physiotherapy practice patterns for patients undergoing surgery for lung cancer – Preliminary results. Respirology 2012, 17 (Supplement 1), page 69, TP113

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Cavalheri V, Jenkins S, Cecins N, Phillips MJ, Sanders LH, Hill K. Patterns of Sedentary Behaviour and Physical Activity Following Curative Intent Treatment for Non-Small Cell Lung Cancer – Preliminary Results. Respirology 2014, 19 (Supplement 2), page 16, TO 012

Cavalheri V, Jenkins S, Cecins N, Phillips MJ, Sanders LH, Hill K. Time Spent in Moderate-to-Vigorous Physical Activity Following Lung Resection for Non-Small Cell Lung Cancer – A Comparison of Absolute and Relative Cut-Off Values. Respirology 2014, 19 (Supplement 2), page 66, TP 036

AWARDS

Best poster presentation - Thoracic Society of Australia and New Zealand (TSANZ)

Awarded at the TSANZ Annual Scientific Meeting 2014 for excellence in the presentation and conduct of research in the area of "Interventional pulmonology and lung cancer".

Travel grant - Thoracic Society of Australia and New Zealand (TSANZ)

Awarded a travel grant for the TSANZ Annual Scientific Meeting 2014.

PhD Top-up Scholarship Award - Lung Institute of Western Australia (LIWA)

Awarded at the Lung Institute of Western Australia Annual General Meeting 2014 for a successful application for a PhD Top-up Scholarship.

CONFERENCE PRESENTATIONS - INVITED SPEAKER

2014:

APA WA Symposium 2014 – Perth, Western Australia

Title: **Lung cancer: The role of exercise training in the early clinical stage**

2013:

Airways 2013 (Boehringer Ingelheim) – Broadbeach, Gold Coast

Title: **Functional performance and physical activity in people with lung cancer**

LIST OF ABBREVIATIONS

6MWD	six-minute walk distance
6MWT	six-minute walk test
ACSM	American College of Sports Medicine
AIHW	Australian Institute of Health and Welfare
ANCOVA	analysis of covariance
ANZCTR	Australian New Zealand Clinical Trials Registry
AT	anaerobic threshold as a percentage of the VO_{2peak}
ATS	American Thoracic Society
BMI	body-mass index
BOCF	baseline-observation-carried forward
bpm	beats per minute
BR	breathing reserve
CG	control group
CI(s)	confidence interval(s)
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise test
CT	computerised tomography
D_LCO	single breath diffusing capacity for carbon monoxide
EG	exercise group
EORTC QLQ-C30	European organisation for research and treatment of cancer quality of life questionnaire core 30
EORTC LC13	Lung cancer subscale of the EORTC QLQ-C30
ERS	European Respiratory Society
EVA	exposure variation analysis
FACIT-Fatigue	functional assessment of chronic illness therapy - fatigue subscale
FACT-L	functional assessment of cancer therapy – lung scale
FEV_1	forced expiratory volume in one second
FRC	functional residual capacity
FT	Fatim Tahirah
FVC	forced vital capacity
GORD	gastro-oesophageal reflux disease
GP	general practitioner
HADS	hospital anxiety and depression scale
HR	heart rate
HRQoL	health-related quality of life
ICC	intra-class correlation coefficient
IPF	idiopathic pulmonary fibrosis
ISWT	incremental shuttle walk test
ITT	intention-to-treat
kg	kilogram
KH	Kylie Hill
L	litre
LLN	lower limit of normal
m	metre
MARCA	multimedia activity recall for children and adults
MCID	minimal clinically important difference

MCS	mental component score (SF-36)
MD	mean difference
METs	metabolic equivalent units
min	minute
ml	millilitre
MLTPAQ	Minnesota leisure time physical activity questionnaire
MMRC	modified medical research council dyspnoea scale
MVV	maximum voluntary ventilation
n	number of participants in the study
NSCLC	non-small cell lung cancer
O_2 pulse	oxygen pulse
PASE	physical activity scale for the elderly
PCS	physical component score (SF-36)
PEDro	Physiotherapy Evidence Database
pred	predicted
RCT(s)	randomised controlled trial(s)
RPE	rate of perceived exertion
RPH	Royal Perth Hospital
RR	relative risk
SAB	SenseWear armband
SAM	Stepwatch activity monitor
SCGH	Sir Charles Gairdner Hospital
SciELO	Scientific Electronic Library Online
SCLC	small cell lung cancer
SD	standard deviation
SE	standard error
SF-36	medical outcomes study short form 36 general health survey
SGRQ	St. George's Respiratory Questionnaire
SMD	standardised mean difference
SpO_2	arterial oxygen saturation measured via pulse oximetry
SPSS	Statistical Package for the Social Sciences
SVC	slow vital capacity
TLC	total lung capacity
TNM	T: primary tumour; N: regional nodes; M: distant metastasis
UK	United Kingdom
USA	United States of America
VATS	video-assisted thoracoscopic surgery
VC	Vinicius Cavalheri
VEmax	maximum minute ventilation
VEmax/MVV	maximum minute ventilation achieved during the cycle ergometry test expressed as a proportion of maximum voluntary ventilation
VO_{2peak}	peak rate of oxygen consumption
W	watts
WHO	World Health Organization
Wmax	maximum work rate (achieved during incremental cycle ergometry test)

CHAPTER 1

INTRODUCTION

This programme of research was designed to:

(i) evaluate the current evidence for exercise training in people following lung resection for non-small cell lung cancer (NSCLC);

(ii) examine current physiotherapy practice patterns for people undergoing lung resection for lung cancer in Australia and New Zealand.

Further, in people following curative intent treatment (i.e. lobectomy with or without adjuvant chemotherapy) for stage I, II or IIIA NSCLC, this programme of research was designed to:

(iii) evaluate impairments and the magnitude of impairments in functional outcomes;

(iv) investigate patterns of sedentary behaviour and physical activity;

(v) compare peak exercise responses as well as patterns of change in exercise responses during the six-minute walk test (6MWT) and the cardiopulmonary exercise test (CPET); and

(vi) investigate the effects of supervised exercise training on recovery of functional outcomes.

The studies were designed to address the following research questions:

1.1 Research questions

1. What is the current evidence for exercise training in people following lung resection for NSCLC?

2. What are the current physiotherapy practice patterns for people undergoing lung resection for lung cancer in Australia and New Zealand?

3. Compared with age and gender-matched healthy controls, are measures of exercise capacity, health related quality of life (HRQoL), peripheral muscle force, physical activity, lung function and feelings of anxiety and depression impaired in people following curative intent treatment for NSCLC?

4. Do patterns of sedentary behaviour and physical activity of people following curative intent treatment for NSCLC differ from those in age and gender-matched healthy controls?

5. Does the 6MWT elicit similar peak exercise responses and patterns of change in heart rate (HR) and arterial oxygen saturation measured via pulse oximetry (SpO_2) as the CPET in people following curative intent treatment for NSCLC?

6. What are the effects of supervised exercise training on exercise capacity, HRQoL, peripheral and respiratory muscle force, physical activity and sedentary behaviour, lung function, functional limitation resulting from dyspnoea and fatigue, and feelings of anxiety and depression in people following lobectomy for NSCLC?

This Chapter provides an overview of the literature pertaining to the development of each research question. The significance of each component in the programme of research is discussed. The order of the research questions is consistent with the order in which Chapters 3 to 8 are presented.

1.2 Question

What is the current evidence for exercise training in people following lung resection for NSCLC?

1.2.1 Background

Lung cancer is an important problem worldwide. Recent data indicates that lung cancer is the most commonly diagnosed cancer in adult males in developing countries, the second most commonly diagnosed cancer in adult males in developed

countries (after only prostate cancer) and the fourth most commonly diagnosed cancer in adult females in both developing and developed countries (1, 2). Mortality from lung cancer is high, with a 5-year survival of 14%, making it the leading cause of death from malignancy in developed countries such as Australia (3), the United States of America (2) and the United Kingdom (4). Non-small cell lung cancer is the most common lung cancer, accounting for approximately 85% of all cases (5). Survival from NSCLC is considerably better than for small cell lung cancer (SCLC). Approximately 40% of people with NSCLC who undergo complete lung resection of the primary tumour survive 5 years (6). In contrast, for people with SCLC, metastasis is common at the time of diagnosis and lung resection is rarely an option. Thus the median survival ranges from 313 to 388 days (7).

Since the early 2000s, there has been an increased interest in outcomes other than survival for people diagnosed with NSCLC. Notably, people with this condition who require lung resection perceive physical debility as a far more important and undesirable outcome than pulmonary complications such as lung collapse and pneumonia (8). Earlier work has demonstrated impairments in exercise capacity in people with lung cancers (9). The reasons for this are likely to be multifactorial. Tumours in the lungs are thought to disrupt pulmonary mechanics and gas exchange (10) resulting in weight loss, anorexia, anaemia, protein catabolism and muscle wasting (11, 12). Dyspnoea and fatigue are also common and likely to result in the adoption of a sedentary lifestyle (13), which serves to further compromise exercise capacity because of skeletal muscle and cardiovascular deconditioning. Treatment for lung cancer compounds the decrements in exercise capacity. Compared with pre-operative measures, peak rate of oxygen consumption (VO_{2peak}) has been shown to be reduced by 13% and 28% 6 months following lobectomy and pneumonectomy, respectively (14). Adjuvant therapy such as chemotherapy initiates a 'deconditioning storm' that further reduces the capacity to deliver or utilise oxygen and substrate during exercise, thereby contributing to exercise intolerance (15).

Another important outcome for people with lung cancer is HRQoL. At the time of diagnosis, people with lung cancer present with impaired HRQoL and considerable psychological distress, such as feelings of anxiety and depression (16, 17). People who have undergone lung resection have demonstrated short-term (4 months) and

long-term (4 years) impairments in HRQoL (18). These impairments were of similar magnitude to those reported by people who have undergone coronary bypass grafting (18).

Exercise training is an intervention that may improve exercise capacity and HRQoL of people following lung resection for NSCLC. The role of exercise training is well established in many chronic respiratory conditions, including chronic obstructive pulmonary disease (COPD) (19), interstitial lung disease (20), cystic fibrosis (21) and asthma (22). There is especially strong evidence for people with COPD. In this population, Cochrane reviews have shown that exercise training improves exercise capacity and HRQoL (19, 23), as well as reduces symptoms of dyspnoea and fatigue (19). There is also evidence to suggest a reduction in healthcare utilisation and a survival benefit, when training is implemented following an acute exacerbation (19, 23). The mechanisms underlying improvements in exercise capacity and exertional dyspnoea relate, at least in part, to a reduction in exercise-induced lactic acidosis due to improved peripheral skeletal muscle oxidative capacity (24, 25).

Systematic reviews have shown that exercise training confers gains in fatigue and HRQoL in people with prostate and breast cancer (26, 27). In people following lung resection for NSCLC, preliminary data from single-group studies have shown that supervised exercise training is feasible, safe and may confer benefits in exercise capacity (28-31) and HRQoL (29). However, to date, a systematic review and meta-analysis of randomised controlled trials (RCTs) analysing the effects of exercise training in people following lung resection for NSCLC is lacking.

1.2.1.1 Significance and novelty of the research

This systematic review and meta-analysis will synthesise the current evidence for exercise training in this population. The review will also identify the strengths and limitations of the RCTs in this area, as well as gaps in the literature. Therefore, the findings will be of use when designing future RCTs to determine the effect of exercise training in people following lung resection for NSCLC.

1.3 Question

What are the current physiotherapy practice patterns for people undergoing lung resection for lung cancer in Australia and New Zealand?

1.3.1 Background

Over the past 8 years, there has been an increase in publications pertaining to the effectiveness of physiotherapy for patients before and after lung resection for lung cancer. Regarding pre-operative management, two recent studies (32, 33) have reported that brief exercise programmes initiated prior to surgery served to decrease the length of hospital stay, suggesting reduced post-operative morbidity and healthcare cost. Further, Jones et al (9) reported that pre-operative exercise training (endurance training using a stationary cycle ergometer) improves cardiorespiratory fitness in patients undergoing pulmonary resection. Specifically, Jones et al (9) demonstrated increases in peak rate of oxygen consumption (VO_{2peak}) and six-minute walk distance (6MWD) (14% and 9%, respectively, both $p < 0.05$) following 14 weeks of cycle ergometry training, undertaken 3 times a week at an intensity ranging from 60% to 70% of the peak work rate. However, these authors did not investigate whether these improvements in exercise capacity were associated with improved outcomes following surgery.

Regarding post-operative management, a study carried out in New Zealand (34), examined the effects of physiotherapy (breathing exercises, ambulation and a progressive shoulder and thoracic cage mobility programme) following pulmonary resection via open thoracotomy on the incidence of pulmonary complications, readmissions to the intensive care unit and length of hospital stay. Participants were randomly allocated to a treatment group (daily respiratory physiotherapy until discharge) or control group (standard medical/nursing care only). This study failed to demonstrate between-group differences in any outcome (34). However an important limitation of this study was that the participants were not characterised by airflow limitation and therefore they were at lower risk of developing a post-operative pulmonary infection (35). It is possible that the role of early post-operative respiratory physiotherapy in reducing post-operative pulmonary complications

following thoracotomy is limited to those with airflow limitation. However, with respect to exercise training following resection, it appears that a supervised programme of moderate intensity exercise in this population is feasible and safe, and may confer benefits in dyspnoea, exercise capacity (28, 29) and HRQoL, particularly among those who do not require concurrent chemotherapy (36).

A survey published in 2007 (37) described the physiotherapy management of patients (not only people with lung cancer) undergoing thoracotomy in hospitals in Australia and New Zealand. Of note, the studies aforementioned were all published after 2007 and at the time the study was conducted there was a lack of data available to guide clinical practice. A new survey would be useful to examine the extent to which findings of the recent studies in this area have been translated into clinical practice.

1.3.1.1 Significance and novelty of the research

The results of the survey will document current physiotherapy practice patterns for people undergoing lung resection for lung cancer. This will: (i) provide information as to whether recent publications in the area have had an impact on clinical practice in Australia and New Zealand; (ii) allow for benchmarking of current practice with other countries and (iii) provide baseline data for the purpose of future comparisons. These comparisons are needed to objectively demonstrate any evolution in the management of lung cancer, such as routine referrals to exercise training programmes.

1.4 Question

Compared with age and gender-matched healthy controls, are measures of exercise capacity, HRQoL, peripheral muscle force, physical activity, lung function, and feelings of anxiety and depression impaired in people following curative intent treatment for NSCLC?

1.4.1 Background

The investigation of impairments and magnitude of impairments in people following curative intent treatment (lung resection with or without adjuvant chemotherapy) for NSCLC would contribute to the determination of specific goals during their post-

treatment rehabilitation. Earlier work that has attempted to quantify impairments in people following curative intent treatment for NSCLC, have focused exclusively on measures of lung function, maximal exercise capacity and HRQoL. Specifically, both lung function and maximal exercise capacity are expected to decrease (14, 38-40), with limited recovery after 6 months (14). Pertaining to HRQoL, a persistent decrease following curative intent treatment is usually seen in people who continue to smoke, have comorbidities, were required to undergo adjuvant chemotherapy or presented with a recurrence of the cancer (41). However, the magnitude of these impairments compared to healthy people remains unknown. Further, it is also unknown whether people following curative intent treatment for NSCLC present impairments in other measures that are likely to be important, such as 6MWD, peripheral muscle force, physical activity, and feelings of anxiety and depression.

The optimal study design to quantify the impact curative intent treatment for NSCLC has on outcomes such as 6MWD, peripheral muscle force, physical activity, and feelings of anxiety and depression would be to collect measures prior to and following treatment. Nevertheless, such a design is difficult to implement in this population as both the patient and the medical team have a major concern in delaying treatment (i.e. lung resection) for further assessments (32, 42). An alternative design, such as comparing measures obtained in people following curative intent treatment for NSCLC with those collected in healthy controls, does not delay the initiation of treatment and is likely to be more feasible in this patient group. Further, as this design ensures that measures of functional capacity collected in healthy controls will be conducted using identical protocols and equipment to those used in people following curative intent treatment for NSCLC, it enables the detection of limits (i.e. thresholds) for normal values for functional capacity.

This study will compare measures made in people following curative intent treatment for NSCLC, with those made in age and gender-matched healthy controls. For those variables from primary functional assessments (exercise capacity, peripheral muscle force and physical activity) which differ significantly between the NSCLC group and healthy controls, data from the healthy controls will be used to calculate the lower limit of normal (LLN). The LLN of a specific outcome measure is the lowest value that can be considered normal for that specific measure (43, 44). The LLNs

calculated will enable the investigation of impairment in specific outcome measures of participants following curative intent treatment for NSCLC relative to age and gender-matched healthy controls.

1.4.1.1 Significance and novelty of the research

This study will demonstrate whether people following curative intent treatment for NSCLC have impairments in exercise capacity, HRQoL, physical activity, peripheral muscle force, lung function, and feelings of anxiety and depression relative to age and gender-matched healthy controls. It will also report the magnitude of any impairment in these outcome measures. This is important for clinical practice as it will allow health professionals to provide people with NSCLC with realistic information regarding impairments and magnitude of impairments they may experience following curative intent treatment. By detecting impairments, the study also has the potential to contribute to the determination of specific goals for post-treatment exercise training.

1.5 Question

Do patterns of sedentary behaviour and physical activity of people following curative intent treatment for NSCLC differ from those in healthy controls?

1.5.1 Background

In both healthy people and patient populations, increased interest has emerged on the role that daily accumulation of sedentary behaviour and participation in physical activity play on health outcomes and on the risk of developing chronic diseases (45-48) . The health benefits of moderate-to-vigorous intensity physical activity (i.e. activities that involve energy expenditure > 3 metabolic equivalent units [METs] (49)) have been extensively reported (50-54). In the general population, regular participation in moderate-to-vigorous physical activity has been shown to produce several health benefits including weight loss, lowered blood pressure, enhanced sensitivity to insulin, lowered concentration of systemic inflammatory biomarkers, preservation of bone mass, improved quality of life and delayed all-cause mortality (53, 54). In patient populations, moderate-to-vigorous intensity physical activity is

also related to health outcomes (55-58) . For instance, in breast cancer survivors, moderate-to-vigorous intensity physical activity is likely to reduce risk of cancer-related mortality (55, 56). Although data on the effects of physical activity in people with lung cancer are scarce, in people with chronic respiratory disease, such as COPD, low levels of moderate-to-vigorous intensity physical activity are related to an increased likelihood of respiratory-related hospital admissions due to exacerbations (57-59). Further, in this population, moderate-to-vigorous physical activity is predictor of mortality, independent of lung function (57).

Although undertaking moderate-to-vigorous intensity physical activity is important, performing tasks at this intensity is likely to represent a small proportion of waking hours. That is, even if person engaged in the recommended 30 minutes per day of moderate-to-vigorous intensity activity (54), time in this activity intensity would constitute only 3% of waking hours for someone who was awake for 16 hours. Therefore, interest is increasing in the impact behaviours and activities < 3 METs (i.e. sedentary behaviour and light intensity physical activity) have on health outcomes.

Sedentary behaviour has been defined both by low energy expenditure (< 1.5 METs) (60) and a sitting or reclining posture (61) throughout waking hours (i.e. sleep is not considered a sedentary behaviour). Common sedentary behaviours include television viewing, reading, driving and computer use. Increased waking hours spent in sedentary behaviour has been related to an increase in waist circumference, higher concentration of triglycerides as well as a clustered metabolic risk score (45-47). That is, sedentary behaviour is a potential risk factor for metabolic diseases such as type-2 diabetes. Importantly, the associations between sedentary behaviour and cardio-metabolic risk factors are independent of the level of moderate-to-vigorous intensity physical activity (45). In addition, the way this time is accumulated is also linked with cardio-metabolic risk factors (47, 62). A cross-sectional study of 4,757 healthy adults (47 ± 14 yr) investigated associations between breaks in sedentary behaviour and markers of cardiovascular disease. A break in sedentary behaviour was considered any transition from sedentary to an active state and was measured using the Actigraph activity monitor. This study demonstrated that an increase in the number of breaks in sedentary behaviour was associated with lower waist

circumference, body-mass index , level of triglycerides and fasting 2-h plasma glucose (62). This research has shaped the public health message of reducing total time in sedentary behaviour and also interrupting sedentary behaviour every 30 minutes with light intensity physical activity (63).

Light intensity physical activity involves energy expenditure ≥ 1.5 and < 3 METs and includes activities such as slow walking, washing dishes, showering and ironing in standing (49, 60). Accumulation of activities in this intensity may also reduce the risk of developing type-2 diabetes and cardiovascular disease (48). Data on 173 Australian adults (mean age [95% confidence interval (CI)] 53 [52 to 56] yr), demonstrated that an increase in the time spent in light intensity physical activity was associated with a lower fasting 2-h plasma glucose (β [95% CI] -0.30 [-0.49 to -0.12]) (48). Importantly, time spent in light intensity physical activity has been shown to be almost perfectly inversely related to time spent in sedentary behaviour (r = -0.96) (45).

Although there has been some research investigating the way in which time in sedentary behaviour and physical activity are accumulated in healthy people (47, 48), people following bariatric surgery (64), people with moderate to severe COPD (65) and females with breast cancer (66, 67), there is no information on patterns of sedentary behaviour and physical activity in people following curative intent treatment for NSCLC.

1.5.1.1 Significance and novelty of the research

Obtaining data on patterns of sedentary behaviour and physical activity of people following curative intent treatment for NSCLC and comparing these data with those collected in healthy controls would be important to assist health professionals to understand the lifestyle adopted by their patients following curative intent treatment for NSCLC. These data would also help health professionals to provide physical activity goals to their patients, aiming at improving health outcomes following curative intent treatment for NSCLC. Further, the findings of this study can also have the potential to stimulate research investigating interventions aimed at changing

negative behaviours towards physical activity in people following curative intent treatment for NSCLC.

1.6 Question

Does the 6MWT elicit similar peak exercise responses and patterns of change in HR and SpO_2 as the CPET in people following curative intent treatment for NSCLC?

1.6.1 Background

Curative intent treatment for NSCLC is associated with marked reductions in exercise capacity (68-71). The CPET is accepted as the gold standard method to quantify exercise capacity and evaluate exercise limitation (72). The CPET is able to provide information pertaining to mechanisms of exercise limitation as it globally assesses exercise capacity by integrating the cardiovascular, pulmonary and musculoskeletal responses to exercise (72). Further, it can be utilised during pre-operative evaluation for thoracic surgery (73, 74) as well as in the prescription of exercise training for cardiopulmonary rehabilitation (24, 75, 76). However, its cost and the sophisticated equipment required to perform the test limit its widespread availability in the clinical setting. In contrast, field-walking tests such as the 6MWT, require much less equipment, and therefore are often used to assess exercise capacity in people undergoing exercise training (77).

The 6MWT measures the maximum distance that a person can cover walking on a flat, hard surface in 6 minutes. It is a self-paced test, however standardised encouragement is given each minute (77). The 6MWT has been shown to be responsive to change following interventions such as exercise training in people with moderate to severe COPD (19), diffuse parenchymal lung disease (78), interstitial pulmonary fibrosis (IPF) (79) and heart failure (80). The 6MWT has also been demonstrated to be responsive to change following lung resection for lung volume reduction surgery (81). Importantly, the 6MWD has been demonstrated to be a predictor of mortality in people with severe COPD (82, 83), IPF (84), and advanced heart failure (85, 86).

Furthermore, the 6MWT can be used to identify patients with COPD who may benefit from using a rollator (e.g. wheeled walker) (87). In pulmonary rehabilitation it can be used to assess the requirement for supplemental oxygen during exercise (88), to prescribe the initial intensity for a walking programme (89) and, due to the moderate to strong relationship between 6MWD and maximum work rate (Wmax) in COPD and IPF, the 6MWD can be also used to prescribe an initial training intensity for cycle-based exercise in these people in the absence of a CPET (90-92).

The current American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation recommends that exercise training intensity be prescribed as a percentage of the peak capacity (e.g. 60% of peak work rate for cycling), in order to maximise physiological benefits (93). Therefore, to determine the usefulness of the 6MWT in prescribing training intensity, it is important to determine whether this test elicits peak exercise responses. Studies in people with moderate to severe COPD, exercise-induced pulmonary hypertension and IPF have compared respiratory and cardiovascular responses during the 6MWT to those during the CPET (92, 94-98). Although differences in the patterns of responses between the two tests were observed, earlier work has reported no difference in VO_{2peak} (94, 95, 97) and either minimal (92) or no difference (94-98) in peak HR between the tests. These results suggested that the 6MWT elicits similar peak exercise responses as the CPET in these patient populations and it is a test that can be used to assess exercise capacity and to prescribe exercise training in people with moderate to severe COPD, exercise-induced pulmonary hypertension and IPF. In people following lung resection (with or without adjuvant chemotherapy) for NSCLC, the 6MWT has been used to prescribe the intensity for a walking training programme and to evaluate changes in exercise capacity following training (31, 36). However, no study has compared the physiological responses elicited during the 6MWT to those elicited during the CPET in this population.

1.6.1.1 Significance and novelty of the research

This study will be an important first step to investigate the physiologic demands of the 6MWT relative to the CPET in people following lung resection for NSCLC. It will also be the first study to examine whether the 6MWT elicits peak exercise

responses in this population and to suggest whether the 6MWT can be used to prescribe exercise training in people following curative intent treatment for NSCLC. Further, this investigation is likely to detect whether the 6MWT is able to offer any additional important insights pertaining to changes in HR and SpO_2, in people following lung resection for NSCLC, that are not provided by the CPET.

1.7 Question

What are the effects of supervised exercise training on exercise capacity, HRQoL, peripheral and respiratory muscle force, physical activity and sedentary behaviour, lung function, functional limitation resulting from dyspnoea and fatigue, and feelings of anxiety and depression in people following lobectomy for NSCLC?

1.7.1 Background

As described previously (1.2.1 Background) the role of exercise training is well established in many chronic respiratory conditions, including COPD (19), interstitial lung disease (20), cystic fibrosis (21) and asthma (22). Preliminary data also suggest that exercise training may play an important role for individuals with a variety of cancer diagnoses (99, 100). For instance, moderate-to-vigorous intensity aerobic exercise training has been demonstrated to have positive effects on cardiovascular fitness both during and after treatment for breast, colon and prostate cancer (99). With regards to breast cancer, a systematic review that included 17 RCTs, on 717 participants, has shown that exercise training resulted in significant improvements in HRQoL, physical functioning, VO_{2peak} and reductions in fatigue (100). Further, in people who have cancers of the ovaries, stomach, prostate or colon, exercise training appears to optimise functional recovery following chemotherapy or radiation therapy (99). However, data demonstrating the effects of exercise training on recovery of functional outcomes specifically in people following curative intent treatment for NSCLC are scant.

Data from single group studies to date suggest that a programme of moderate intensity exercise training in people following curative intent treatment is feasible and safe and may confer benefits in dyspnoea, exercise capacity (30, 31) and HRQoL, particularly among those who do not require concurrent chemotherapy (28,

29). Two published RCTs have investigated the effects of exercise training specifically in people following lung resection for NSCLC (36, 101). Arbane et al (36) provided a twice-daily in-patient exercise programme for 5 days plus 12 weeks of home-based exercises for 26 people following lobectomy for NSCLC. The findings of this study showed that exercise maintained quadriceps muscle force during the immediate post-operative period (5 days post-operatively), whereas the quadriceps muscle force of the control group decreased during the same period (36). However, after the 12 weeks of intervention, compared to the control group, no improvements were demonstrated in HRQoL, exercise capacity or quadriceps muscle force in the group that received the 12-week home-based exercise programme. Stigt et al (101) provided a twice a week, 12-week programme of exercise training, that commenced 4 weeks after hospital discharge, for 23 people following lung resection for NSCLC. Although no differences in HRQoL and pain levels were found between the exercise training and control groups, this RCT showed that the exercise training group improved 6MWD by 35 m, whereas the 6MWD of the control group decreased 59 m in the same period of time (101).

Notably, both RCTs have methodological limitations. Specifically, in the RCT by Arbane et al (36) the 12-week exercise programme was home-based and unsupervised. Although there is a lack of studies comparing the effectiveness of supervise *versus* unsupervised exercise training in people with NSCLC, literature in people with COPD have already demonstrated that the magnitude of improvement in exercise capacity is substantially larger in people who undergo supervised exercise training (102). Of note, VO_{2peak} of people with COPD has been shown not to increase following unsupervised exercise training (102). Further, in the RCT by Arbane et al (36) there was only partial blinding of outcome assessment (i.e. in 10 participants, the same therapist performed the treatment and assessments), increasing the risk of performance bias. In the RCT by Stigt et al (101), all the participants underwent lung resection via an open thoracotomy. As nowadays video-assisted thoracoscopic surgery (VATS) is preferred over thoracotomy for people with clinical stage I NSCLC (103), findings from that study might not be representative of the best current practice. Additionally, Stigt et al (101) assessed HRQoL using a generic questionnaire. As generic HRQoL questionnaires are less responsive to change than

disease-specific questionnaires, the findings pertaining to HRQoL of that study should be interpreted with caution.

The two aforementioned RCTs reported that attrition was an important barrier to their studies (36, 101). Additionally to their relative small sample sizes (ranging from 23 to 27 participants in each group), the two RCTs reported considerable attrition rates (36, 101). For instance, the loss to follow-up for the quadriceps muscle force assessment (i.e. post-intervention minus baseline) in the study by Arbane et al (36) was 34% for the exercise training group and 48% for the control group. In the study by Stigt et al, the loss to follow-up for the exercise capacity assessment (i.e. 3 months minus baseline) was 65% for the exercise training group and 56% for the control group.

In order to address the limitations of the abovementioned RCTs and to improve the quality of data on the effects of exercise training for people following lung resection for NSCLC, RCTs with more rigorous methodology are warranted.

1.7.1.1 Significance and novelty of the research

This RCT will demonstrate the effects of supervised exercise training on several outcome measures following curative intent treatment for NSCLC. It will also attempt to address the limitations of the previously mentioned RCTs by providing a supervised exercise training programme, including both people who underwent open thoracotomy (with or without adjuvant chemotherapy) and people who underwent VATS (with or without adjuvant chemotherapy), blinding the outcome assessor and using both disease-specific and generic questionnaires to assess HRQoL. The findings of this study will have the potential for an immediate impact on clinical practice. This is because exercise training programmes for people with lung disease exist in many countries throughout the world and therefore, if exercise training is shown to be effective, the study findings will provide evidence base to promote the referral of patients following surgical resection to existing exercise training programmes.

CHAPTER 2

LITERATURE REVIEW

Overview

This literature review is divided into four parts.

Part 1 is an overview on lung cancer and comprises information pertaining to incidence and mortality, risk factors, symptoms, economic burden and the impact lung cancer has on families and caregivers.

Part 2 outlines the staging system for the two types of lung malignancies: (i) small cell lung cancer (SCLC) and (ii) non-small cell lung cancer (NSCLC). This section includes some differences between the two types, specific characteristics of NSCLC and also describes treatment options for people with NSCLC (i.e. surgery, chemotherapy, radiotherapy, targeted therapy and palliation).

Part 3 discusses the impact of lung resection for NSCLC on outcomes such as lung function, exercise capacity, health-related quality of life as well as physical activity and sedentary behaviour and describes measurement options and variables for each of these outcomes.

Part 4 explores the role of physiotherapy and exercise training following lung resection for NSCLC. An extension of this part is presented in Chapter 3, which is a Cochrane systematic review on exercise training following surgery for NSCLC undertaken as part of this doctoral programme of research. The protocol of this review was published in *The Cochrane Library in 2012* (104). The full version of the review was published in *The Cochrane Library in 2013* (105). This review was co-published in 2014 in Cancer Treatment Reviews (106).

Part 1

2.1 Introduction

Primary lung cancer has been defined as a malignant tumour starting in the tissue of one or both lungs (3). Lung carcinomas can originate anywhere in the lungs, including the trachea, bronchi, bronchioles and alveoli. They occur when lung cells become abnormal and present as an uncontrolled growth resulting in a mass called a tumour or neoplasm (3). Tumours can be benign (i.e. not cancerous) or malignant (i.e. cancerous). Benign tumours do not spread to other parts of the body, although, as they grow, they may interfere with other body organs and tissues. A malignant tumour is characterised by its ability to metastasise, that is, the ability to spread elsewhere in the body. If the spread is not prevented, complications arise that will inevitably result in death (3, 107).

2.1.1 Incidence and mortality

Pulmonary malignancy is an important problem worldwide. Recent data indicates that lung cancer is the most commonly diagnosed cancer in adult males in developing countries, the second most commonly diagnosed cancer in adult males in developed countries (after only prostate cancer) and the fourth most commonly diagnosed cancer in adult females in both developing and developed countries (1, 2). Mortality from lung cancer is high and depends largely on type, anatomical staging as well as histological classification of the tumour. The overall ratio of mortality to incidence for lung cancer is 86%, making it the leading cause of death from malignancy in developed countries such as Australia (3), the United States of America (USA) (2) and the United Kingdom (UK) (108).

The incidence of lung cancer has been decreasing over the past 3 decades in males whereas, in women, rates have been increasing since the early 1990's (109). In Australia, between 1982 and 2007, lung cancer incidence decreased by 32% in men whereas in women the incidence increased by 72% (110). This discrepancy in the incidence of lung cancer between genders appears to be due to differences in the single greatest risk factor for development of the disease; cigarette smoking (109). The incidence of lung cancer in males within Australia peaked around 1980, which

was approximately 20 to 25 years after the peak rates of tobacco consumption were reported (111). Cigarette smoking in women peaked about 30 years later than in men and thus the incidence of lung cancer in Australian women continues to increase (111).

2.1.2 Risk factors

A risk factor is any factor that is associated with an increased chance of developing a particular health condition. Cigarette smoking (including passive smoking), air pollution, occupational exposure, alcohol consumption, underlying lung disease and family history of lung cancer are some of the risk factors for lung cancer (112).

2.1.2.1 Cigarette smoke and the impact of anti-smoking campaigns

Cigarette smoking is the most important risk factor in the development of lung cancer in both men and women (112). Duration as well as number of cigarettes a person smokes are strongly associated with the risk of developing lung cancer (3). In Australia, roughly 90% of lung cancers in males and 65% in females are due to cigarette smoking (3). The very first study showing that smoking was linked to lung cancer was conducted in 1912 by Dr. Isaac Adler (113). However, the first researchers who were credited with demonstrating that there was a true association between cigarette smoking and lung carcinoma were Dr. Richard Doll and Professor Austin Bradford Hill (114) in 1950. They interviewed 709 people with lung cancer (649 men) and 709 people (649 men) with diseases other than lung cancer, who were used as a control group. The proportion of non-smokers in the two groups was significantly different ($p < 0.02$). Only two men (0.3%) and 19 women (32%) with lung cancer were non-smokers whereas, in the control group, 27 men (4%) and 32 women (53%) were non-smokers. Further, both the number of cigarettes smoked daily as well as the total number of years a person had smoked were demonstrated to be higher in the group with lung cancer (114).

There are more than 60 established carcinogens amongst the identified chemicals in cigarette smoke and duration as well as number of cigarettes smoked have been reported as the strongest determinants of lung carcinoma in smokers (115). The more someone smokes the higher is the risk for developing and dying from lung cancer

(115). A prospective study of 42,722 people has shown that people who smoke 1 to 4 cigarettes per day have 3 to 5 times the risk of dying from lung cancer compared with never-smokers (116). Those who smoke 8 to 12 cigarettes per day have around 12 times the risk of dying from lung cancer (117) and a 50-year follow-up study (118) reported that people who smoke 25 or more cigarettes a day have 24 times the risk of compared with lifelong non-smokers.

Anti-smoking campaigns were initiated in Australia in the 1960s (119, 120). However, the first tobacco control campaign fully funded by the federal government was initiated in 1997 (121). Prior to this, anti-tobacco campaigns were developed, funded and implemented within each state and territory. The proposal for the first national campaign originated after an apparent stalling of the steady decline in the prevalence of smoking that had occurred in the late 1980s and early 1990s. That is, between 1983 and 1989 the proportion of regular smokers in Australia had reduced from 35% to 28% (122). However, between 1989 and 1995, the proportion of Australians who were regular smokers had not changed substantially (28% vs. 26%).

An estimate of the number of Australians aged between 15 and 64 years who quit smoking due to the campaign initiated in 1997 was 190,000 (121). More importantly, the predicted cases of lung cancer and deaths for lung cancer avoided were 10,134 (9,815 to 10,454) and 9,872 (9,556 to 10,187), respectively. The saving to healthcare was estimated to be approximately $160 million (123). Data from the Australian Institute of Health and Welfare (AIHW) showed that, in 2010, 15% of Australians aged 14 years or older were daily smokers (124). This compares favourably with data collected in 1983, 1991 and 2001, revealing that the proportion of daily smokers in Australia was 35%, 26% and 23%, respectively. Further, between 1991 and 2010 the number of Australians who had never smoked increased from 49% to 58% (124).

2.1.2.2 Other risk factors

Air pollution, occupational exposure and alcohol consumption have also been shown to be associated with a greater risk of developing lung cancer. That is, an urban setting characterised by emissions rich in various polycyclic aromatic hydrocarbon compounds, a work setting full of crystalline silica and chrysotile asbestos and an

alcohol consumption of more than 30g/day have been associated with an increased risk for lung malignancies (112, 125-127).

A systematic review of 91 studies has shown that a history of lung disease such as chronic obstructive pulmonary disease (COPD), pneumonia and tuberculosis is associated with an increased risk of lung cancer (128). Specifically, in people with COPD, the combined relative risk (RR) of lung cancer was 1.83 (95% confidence interval [CI]: 1.60 to 2.11). In people who had pneumonia or tuberculosis, the RR of lung cancer was 1.43 (95% CI: 1.22 to 1.68) and 1.76 (95% CI: 1.49 to 2.08), respectively. Increased risk of developing lung cancer was also detected among never smokers with a previous history of pneumonia (RR = 1.36; 95% CI: 1.10 to 1.69) and tuberculosis (RR = 1.90; 95% CI: 1.45 to 2.50), supporting a direct relationship between a history of lung disease and lung carcinoma (128). It is still unknown whether it is the inflammatory process or the pathogenesis of the lung diseases that increase lung cancer risk.

Family history of lung cancer has been shown to be a strong predictor of lung malignancy risk (129). A multi-centre case-control European study conducted in 16 centres across seven countries confirmed this finding reporting a 1.5-fold higher risk of lung cancer among men and a 1.73-fold higher risk of lung cancer among women with a family history of lung cancer (130). This study also demonstrated that lung cancer risk was 40% higher among never-smokers who had family history of lung cancer. Additionally, a 1.6-fold higher risk of developing lung cancer has been shown among people whose first-degree relatives had the disease. A genetic component for lung cancer has been proposed based on familial studies (129, 131, 132), however, progress in identifying specific susceptibility genes has been slow.

2.1.2.3 Physical activity as a protective factor

The role that participation in physical activity has on reducing the incidence of cancer in both smokers and non-smokers has been reported in the literature since the early to mid 1980's (133-135). However, one of the first published papers that hypothesised the presence of a relationship between low levels of physical activity and cancer was published in 1922 by Sivertsen and Dahlstrom (136). The study

suggested that the death rate was lower in people whose occupation involved a large amount of muscular activity than in people whose occupation involved very little muscular activity. In a retrospective analysis they divided people in six different groups based on muscular activity required by their occupations. An important finding was that office workers had a 2-fold higher death rate due to lung cancer compared to people whose occupation required great muscular activity (e.g. blacksmiths and miners) (136). In keeping with this early study, in 1989 Albanes et al (137) published a retrospective study where they reported an association between self-reported physical activity and the incidence of colorectal, prostate, breast and lung cancer. They included data from 12,545 participants who were divided into two groups. The first group included people who reported being "quite inactive" during their usual day and engaging in little physical activity during their recreational hours. The second group, people who reported being "very or moderately active" during their usual day and undertaking a moderate amount of physical activity during their recreational hours. The study demonstrated an increased risk of cancer among people in the first group when compared to the second group (RR 1.8 [95% CI: 1.4 to 2.4] for men; RR 1.3 [95% CI: 1.0 to 1.8] for women). More importantly, the lungs were one of the sites that showed a stronger inactivity-cancer relationship (RR 1.6 [95% CI: 1.2 to 3.5]).

Supporting and confirming the results of the abovementioned studies, a meta-analysis of nine studies (two case-control and seven cohort studies) demonstrated that physical activity protects men and women against cancer (138). Based on studies that utilised questionnaires and interviews to define mild, moderate and high levels of physical activity, the authors suggested a reduction of 25% and 38% in the risk of developing lung cancer in men and women, respectively, through engaging in high levels of physical activity rather than mild levels (138). Following this earlier work, the American Cancer Society recommended the adoption of a physically active lifestyle defined as 30 minutes per day for adults and 60 minutes per day for children and adolescents of moderate activity, 5 days per week (139).

2.1.3 Symptoms and late diagnosis

Cancers such as breast and prostate metastasise to a relatively limited number of sites and this process can take years to occur. Conversely, lung cancer quickly spreads to multiple sites. Nevertheless, the high mortality rate in people with lung cancer is not only due to this rapid spread compared to breast and prostate cancer (140), but also to late diagnosis (141).

Around 90% of people present with symptoms at the time they are diagnosed with lung cancer. Typically individuals report 2 or 3 symptoms at the time of diagnosis (141). The most frequently reported symptoms are cough, dyspnoea, chest pain, and haemoptysis as well as systemic symptoms such as weight loss, anorexia and asthenia (142). The literature has shown that patients often seek medical attention after been symptomatic for several months (143, 144). Regardless of their disease stage, patients often fail to recognise the danger of "simple" symptoms (145) such as cough, which has been shown to be the most common presenting symptom (141).

In addition to the delay by the patients in seeking medical attention, there is also the medical system delay that contributes to late diagnosis. This second source of delay specifically encompasses delay by the general practitioner (GP) in arranging further investigation and referral to a specialist (146) as well as delay by the specialist who relies on other medical professionals such as pathologists and radiologists to determine the diagnosis and treatment. Delays within the medical system have been reported to be longer than the delay by the patient in seeking medical attention (147). In a Swedish sample from 2002, the median time from first symptom(s) until treatment or the decision not to treat (the sum of all delays) was demonstrated to be 189 days (i.e. 6 months) (147). A more recent research carried out in Denmark showed better numbers for the sum of all delays (median [95% CI]: 98 [57 to 168] days) (148). Nevertheless the Danish research confirmed what had been demonstrated in the Swedish study. Patient delay was reported to be 21 [7 to 56] days whereas the system delay was reported to be 55 [32 to 93] days (148).

2.1.4 Economic burden

Regarding the economic burden, the cost of treating a lung carcinoma is high. This high cost is related to the number of cycles of chemotherapy as well as the use of radiotherapy and surgery (149). Lung cancer treatment cost is responsible for 20% of Medicare's total expenditures for cancer in the USA (150). It is ranked the second highest cost for treatment among cancers, behind pancreatic cancer (151). A retrospective study carried out in America that was published in 2005 (152) included 2,040 people with lung cancer and 6,120 controls and showed that the monthly total expense with medical care (i.e. hospital admissions, emergency room, outpatient office visit, radiology, laboratory and drugs) was USD$6,520 for patients *versus* USD$339 for controls. The overall costs across the study period (from diagnosis to death or maximum of 2 years) were USD$45,897 for patients and US$2,907 for controls. To the extent of our knowledge, Australian equivalent data for costs are not available.

Due to the premature retirement from employment by people with lung cancer, family caregivers are inevitably affected (75). Relative to other cancers, lung carcinoma has been shown to have the greatest economic impact on families due to its high functional burden and poor prognosis, resulting in expensive treatments (150, 151, 153). A recent study has demonstrated that loss of involvement in social and leisure activities as well as reduced employment hours are the two changes most frequently reported by caregivers (154). Further, one fifth of the caregivers who participated in the aforementioned study lost their jobs or spent most of their savings during the course of their relative’s illness (154). This issue emphasises that action has to be taken to ameliorate financial support and address practical concerns of both patients and their family caregivers during lung cancer treatment.

Part 2

2.2 Staging and types of lung cancer

One of the first attempts to develop a classification system for carcinomas of the lungs was published in 1924 (155). This publication remains the basis of the current document used by the World Health Organisation to classify lung tumours (156). Basically, the two main types of lung cancer are SCLC and NSCLC and they are both staged using the same staging system: the TNM (T: primary tumour; N: regional nodes; M: distant metastasis) (157).

2.2.1 Staging malignant tumours

The TNM Classification of Malignant Tumours was developed by Pierre Denoix between 1943 and 1952 (158) and it is currently in its seventh version (159). The system takes into consideration (i) the size of the original tumour and whether nearby tissue has been invaded (T), (ii) the involvement of regional lymph nodes (N) and (iii) whether metastasis has occurred (M).

2.2.1.1 The descriptor T

The primary tumour can be described as: (i) TX: malignant cells in sputum or bronchial washings that cannot be detected via imaging or bronchoscopy; (ii) T0: no evidence of primary tumour; (iii) Tis: carcinoma *in situ*; (iv) T1: tumour ≤ 3cm in its greatest dimension; (iv) T2: tumour > 3cm but < 7cm or tumour with any of the following features: involvement of main bronchus; ≥ 2cm distal to the carina; invasion of visceral pleura; atelectasis or obstructive pneumonitis extending to hilar region; (v) T3: tumour > 7cm or direct invasion of any of the following: chest wall; diaphragm; mediastinal pleura; phrenic nerve; parietal pericardium, and (vi) T4: tumour of any size invading any of the following: mediastinum; great vessels; heart; trachea; carina; esophagus; recurrent laryngeal nerve; vertebral body.

2.2.1.2 The descriptor N

Regional lymph nodes can be classified as: (i) NX: regional lymph nodes cannot be assessed; (ii) N0: no regional lymph node metastasis; (iii) N1: metastasis in

ipsilateral-peribronchial and/or ipsilateral-hilar lymph nodes and intrapulmonary nodes; (iv) N2: metastasis in ipsilateral-mediastinal and/or subcarinal lymph node(s) and (v) N3: metastasis in contralateral-mediastinal, contralateral-hilar, ipsilateral or contralateral-scalene, or supraclavicular lymph node(s)

2.2.1.3 The descriptor M

Metastasis can be classified as: (i) MX: distant metastasis cannot be assessed; (ii) M0: no distant metastasis; (iii) M1a: separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericardial) effusion; (iv) M1b: distant metastasis.

2.2.1.4 The TNM categories

There are seven different stages of a lung malignancy (IA, IB, IIA, IIB, IIIA, IIIB and IV). The TNM staging is used to define the seven stages, which are summarised in Table 2-1.

Table 2-1: TNM subsets

Stage	TNM Subset
IA	$T_{1a}\ N_0\ M_0$ $T_{1b}\ N_0\ M_0$
IB	$T_{2a}\ N_0\ M_0$
IIA	$T_{2b}\ N_0\ M_0$ $T_{1a}\ N_1\ M_0$ $T_{1b}\ N_1\ M_0$ $T_{2a}\ N_1\ M_0$
IIB	$T_{2b}\ N_1\ M_0$ $T_3\ N_0\ M_0$
IIIA	$T_3\ N_1\ M_0$ $T_{1a}\ N_2\ M_0$ $T_{1b}\ N_2\ M_0$ $T_{2a}\ N_2\ M_0$ $T_{2b}\ N_2\ M_0$ $T_3\ N_2\ M_0$ $T_4\ N_0\ M_0$ $T_4\ N_1\ M_0$
IIIB	$T_4\ N_2\ M_0$ $T_{1a}\ N_3\ M_0$ $T_{1b}\ N_3\ M_0$ $T_{2a}\ N_3\ M_0$ $T_{2b}\ N_3\ M_0$ $T_3\ N_3\ M_0$ $T_4\ N_3\ M_0$
IV	Any T, any N and $M_{1a/1b}$

Abbreviations: T – Tumour; N – Lymph node; M – Metastasis.

Treatment options as well as prognosis differ considerably across the seven possible stages. Literature pertaining to incidence, prevalence, treatment and prognosis of each stage of lung cancer will be discussed in the next sections.

2.2.2 Small cell lung cancer

Small-cell lung cancer accounts for only 15% of new cases each year (160). However it is responsible for 25% of deaths from lung cancer (160). In Australia, data from 2007 showed that SCLC accounted for approximately 12% of all lung cancer diagnoses (3). The main known cause of SCLC is cigarette smoking, accounting for roughly 95% of cases (160). Compared to NSCLC, SCLC is more invasive and life-threatening. For people with SCLC, the median survival following diagnosis ranges from 313 to 388 days (7).

Metastasis is common at the time of diagnosis of SCLC and surgical resection is rarely an option (160). As the focus of this thesis is on exercise training for people undergoing lung resection for lung cancer, people with SCLC were not included in the studies described in this thesis. Therefore, this literature review focuses on the available literature pertaining specifically to NSCLC.

2.2.3 Non-small cell lung cancer

From a histological perspective, NSCLC is the most common type of lung cancer, accounting for approximately 85% of all cases (5). The histological subtypes, firstly proposed by Marchesani in 1924 (161), are still the basis for the current World Health Organization (WHO) classification (162). Marchesani described three subtypes of NSCLC: (i) adenocarcinoma, (ii) squamous cell carcinoma and (iii) large cell carcinoma. Their differences are particularly influenced by the evolution of the worldwide epidemic of smoking-related lung cancer (163).

Adenocarcinomas account for approximately 31% of all lung cancers (164). This subtype is typically peripheral with a diameter of less than 4 , at the time of diagnosis, 51% chest radiographs show hilar or mediastinal lymphadenopathy (165). Squamous cell carcinomas account for nearly 30% of lung carcinomas and in over 90% of cases occur in cigarette smokers. They are typically centrally located and

often larger than 4 cm in diameter (166). Finally, large cell carcinomas account for 9% of all lung cancers (164) and typically present as large peripheral masses. They often present a rapid growth and can metastasise to the mediastinum and brain (167).

Survival from NSCLC is considerably better than for SCLC. For people with NSCLC who are considered eligible for complete surgical resection of the primary tumour (i.e. stages I, II and IIIA), survival is approximately 40% at 5 years (6). Specifically, 5-year survival rates for each clinical stage are as follows: IA – 61%; IB – 38%; IIA – 34%; IIB – 24%; IIIA – 13%; IIIB – 5% and IV – 1% (168). Treatment options as well as prognosis and mortality vary based on the TNM staging and will be presented in the next section.

2.2.3.1 Treatment of NSCLC

2.2.3.1.1 Treatment of stage I and II NSCLC

People with stage I or II NSCLC are in the early stage of the disease. Although cure cannot be guaranteed, a curative approach is the therapy of choice for early stages. Surgical resection of the tumour is considered to be the preferred treatment of stage I and II NSCLC (103).

In order to determine suitability for surgery pre-operative evaluation comprises measures of pulmonary function, such as forced expiratory volume in one second (FEV_1) and single breath diffusion capacity for carbon monoxide (D_LCO) as well as the prediction of post-operative values for these variables. These assessments are recommended in all people undergoing lung resection (169). For people with an FEV_1 below 1.5 litres, or either FEV_1 and/or D_LCO below 80% of the predicted value in healthy individuals, or either predicted post-operative FEV_1 and/or predicted post-operative D_LCO below 30% of predicted values, a cardiopulmonary exercise test (CPET) is recommended to assist in refining the magnitude of peri-operative risk (169). Those who have a peak rate of oxygen uptake (VO_{2peak}) of > 20 $ml \cdot kg^{-1} \cdot min^{-1}$ (or 75% of the predicted normal value) are often deemed eligible for pneumonectomy. Those with a VO_{2peak} between 10 and 20 $ml \cdot kg^{-1} \cdot min^{-1}$ or (35% to 75% of the predicted normal value) may be eligible for lobectomy (73). When CPET is not available, a stair climbing test can be used as a surrogate (170-172). The cut-

off of 22 m (i.e 142 steps of 0.155 m) has been shown to have a positive predictive value of 86% to predict a VO_{2peak} of 15 $ml \cdot kg^{-1} \cdot min^{-1}$ (173). Therefore, people who are able to climb > 22 m are regarded to be at a low risk for developing complications following lung resection (172).

Although people in stage I NSCLC do not benefit from adjuvant chemotherapy (i.e. post-operative chemotherapy) (174-176), the use of adjuvant chemotherapy for stage II NSCLC is recommended as it has been demonstrated to provide a 10% higher overall 5-year survival (177). The American College of Chest Physicians recommend that all patients should have systematic mediastinal lymph node sampling at the time of lung resection (103), so that adjuvant chemotherapy can be prescribed if any nodes are found to have been affected. Post-operative radiotherapy has been shown to be associated with worse survival in people with stage I and II NSCLC (178) and it is not recommended as part of the post-operative approach.

For people deemed not eligible as well as for those who decline surgical resection, radiotherapy is recommended. Radiotherapy has been demonstrated to provide survival benefit (9% increase in 2-year survival) (179) and remains the primary curative intent approach in such cases. Insufficient evidence exists however, to recommend routine use of chemotherapy along with radiation for the treatment of people with inoperable stage I and II NSCLC (180). Ablative modalities such as the radiofrequency ablation (a minimally invasive technique) have been used in medically inoperable people with small peripheral tumours (< 3 cm) yet, further studies are needed to define the role of ablative therapies in the treatment of such individuals (103).

2.2.3.1.2 Treatment of stage III NSCLC

Stage III NSCLC is a rather heterogeneous stage. It ranges from resectable tumours with microscopic nodal metastasis to unresectable tumours with bulky nodal metastasis. A combination of chemo and radiotherapy is the treatment of choice for people in this stage. A good performance status, defined as a score 0 (i.e. fully active) to 1 (i.e. only limited in vigorous physical activity) out of 5 on the Eastern

Cooperative Oncology Group scale (181), with minimal weight loss can be definitive for a positive treatment outcome (182).

For people with good performance status, minimal weight loss and operable T1-3, biopsy proven N2 and M0 NSCLC (stage IIIA), surgery has not been shown to increase overall survival (183). Nonetheless, Albain et al (183) compared chemo/radiotherapy alone with chemo/radiotherapy plus surgical resection of the tumour and nodes, and demonstrated that, at 5 years, 22% of participants in the chemo/radiotherapy plus surgery arm were disease-free compared with 11% of participants in the chemo/radiotherapy arm. This finding underpins the reasoning behind the Cancer Council Australia stating that induction chemo/radiotherapy followed by surgery is feasible and improves progression-free survival in selected people with clinical IIIA (N2) disease (180).

2.2.3.1.3 Treatment of stage IV NSCLC

Stage IV NSCLC is not curable however, it is treatable. Stage IV includes people with intra-thoracic or extra-thoracic metastatic disease and the aim of the treatment of people in this stage is palliation, both through improvement of symptoms and quality of life as well as prolonging survival (184).

Both the American College of Chest Physicians and the Cancer Council Australia recommend the use of platinum-based chemotherapy to extend survival in people with stage IV NSCLC (180, 184). In those with a good performance status, stable co-morbidities, adequate organ function and without uncontrolled cerebral metastases, platinum-based chemotherapy has been shown to improve quality of life and prolong survival by 10% at one year compared with best supportive care (185).

Pertaining to palliative thoracic radiotherapy, Lester et al (186) have shown that it is effective in relieving symptoms due to primary lung cancer. The main symptoms relieved by thoracic radiotherapy are cough (20 to 65% of people improved), dyspnoea (40 to 55% of people improved), chest pain (39 to 80% of people improved) and haemoptysis (39 to 95% of people improved) (187, 188).

Part 3

2.3 Impact of lung resection in people with NSCLC

As discussed in the previous section (i.e. 2.2.3.1 Treatment of NSCLC), lung resection is the preferred treatment for people in early stage NSCLC (103). Although lung resection is associated with post-operative pulmonary complications such as lung collapse, pneumonia and prolonged mechanical ventilation, people with lung cancer perceive the likelihood of a physical debility as far more important and undesirable than pulmonary complications (8). The focus of this section is a description of the impact lung resection (with or without adjuvant chemotherapy) has on the important outcomes of lung function, exercise capacity, health-related quality of life (HRQoL), symptoms of pain, fatigue and dyspnea, physical activity, muscle force and feelings of anxiety and depression. Where possible, a comparison between the magnitude of impairment following different types of resection (e.g. lobectomy or pneumonectomy) as well as different surgical techniques is discussed.

2.3.1 Lung function

Lung function has consistently been shown to decrease after lung resection for NSCLC, regardless of the surgical technique (open thoracotomy or video-assisted thoracoscopic surgery [VATS]) (189, 190). Measures such as the FEV_1, forced vital capacity (FVC), total lung capacity (TLC) and D_LCO are decreased following thoracic surgery and demonstrate limited recovery at 3 to 6 months after lung resection. Compared with pre-operative measures, FEV_1, FVC, TLC and D_LCO have been shown to be reduced by 11%, 11%, 12% and 8%, respectively, 3 months after lobectomy (38). Deficits persisted with reductions of 9%, 7% and 10% in FEV_1, FVC and TLC, respectively, 6 months following lobectomy (38). Following pneumonectomy, the same study (38) showed that 6 months after the surgical removal of the lung, all measures of lung function were decreased by 30%. Nezu et al (14) demonstrated that vital capacity (VC) decreased 12% and 40% following lobectomy and pneumonectomy, respectively, and also reported similar decrements in FEV_1 at 6 months after lobectomy and pneumonectomy (11% and 36%, respectively).

Conversely, in those people with NSCLC and moderate to severe COPD, neither FEV_1 nor D_LCO changed following lobectomy (191). The explanation for this may be that, despite losing lung parenchyma, having part of their lungs removed reduced airflow obstruction and pulmonary hyperinflation, leading to less air trapping and improved chest wall and diaphragm mechanics (192, 193).

2.3.2 Exercise capacity

2.3.2.1 Laboratory-based maximal incremental cardiopulmonary exercise test

The CPET, commonly performed on a cycle-ergometer, provides information pertaining to maximal and submaximal exercise capacity as well as a global assessment of the responses of the respiratory, cardiovascular and musculoskeletal systems to exercise (72). It is a symptom-limited maximal incremental exercise test used worldwide to evaluate people with respiratory and cardiovascular conditions with the goal of diagnosing the pathophysiological causes of exercise intolerance. The results also play an important role in determining suitability for lung resection. Measures of respiratory gas exchange such as the rate of oxygen uptake (VO_2), carbon dioxide output and minute ventilation are derived during the test in addition to heart rate, blood pressure and arterial oxygen saturation. Peak rate of oxygen uptake (VO_{2peak}) is the most commonly reported variable of maximal exercise capacity in studies of people with NSCLC as it has been demonstrated to be a predictor of post-operative pulmonary complications as well as an independent predictor of mortality following lung resection for NSCLC(194). As VO_2 increases linearly with work rate (195), maximum work rate (Wmax) is also a commonly reported variable.

2.3.2.2 Field-based exercise tests

Field-based exercise tests are an easy, affordable and valid way to measure exercise capacity in clinical settings where the CPET is not available. To date, the most commonly applied field-based tests of exercise tolerance in people with respiratory conditions are the six-minute walk test (6MWT) and the incremental shuttle walk test (ISWT).

2.3.2.2.1 Six-minute walk test

The 6MWT is a practical simple test that does not require expensive exercise equipment or advanced training for technicians (77). This test measures the maximum distance (6MWD) that a person can cover walking on a flat, hard surface in 6 minutes. It is a self-paced test, however standardised encouragement is given every minute (77). Reference equations to predict 6MWD in Australian adults have been published by Jenkins et al (196).

In people with moderate to severe COPD, patterns of physiological responses during a 6MWT have been shown to be alinear in contrast to responses during a CPET (94). Both heart rate and VO_2 rapidly increase during the first 3 minutes of a 6MWT, reaching a plateau after the third minute. However, the 6MWT has been demonstrated to elicit peak heart rate and VO_{2peak} similar to those elicited during a CPET in people with moderate to severe COPD (94, 95). Studies investigating the patterns of response to the 6MWT in people with NSCLC are yet to be published.

2.3.2.2.2 Incremental shuttle walk test

The ISWT test has been designed to stress a person to a symptom-limited maximum performance (197). It is an incremental and continuous walking test in which the person walks around two cones, placed 10 m apart, with the speed of walking dictated by an audio signal. The test has 12 levels and the speed increases each minute. The test is terminated if the individual is either unable to continue walking due to symptoms or unable to maintain the required speed (197).

Similar to the CPET, heart rate and VO_2 during the ISWT increase linearly (94). The ISWT has also been demonstrated to elicit peak heart rate, VO_{2peak} and symptoms of dyspnoea comparable to those elicited during a CPET in people with moderate to severe COPD (94, 96).

2.3.2.3 Exercise capacity following lung resection for NSCLC

Lung resection is associated with marked reductions in maximal exercise capacity (68-71). One of the first studies to demonstrate these reductions was published by in 1990 (69). These researchers reported the Wmax, achieved during a cycle-ergometer

test, in 47 people with lung cancer, before and 2 months after surgery. A total of 27 participants had undergone lobectomy and 20 had undergone pneumonectomy. The magnitude of reduction in Wmax in the group which received lobectomy was 12% (77 ± 21 W to 67 ± 20 W), whereas the pneumonectomy group reduced their Wmax by 26% (78 ± 25 W to 58 ± 28 W) 2 months after lung resection. In a later study, Nezu et al (14) assessed 82 people before and after lung resection for lung cancer (60 underwent lobectomy and 22 underwent pneumonectomy). Six months following lung resection, there was a decrease in VO_{2peak} of 13% and 28% in the lobectomy and pneumonectomy groups, respectively. Wang et al (40) followed a group of people who underwent lung resection for lung cancer over a longer time period. They compared exercise capacity measured 12 months following lung resection with pre-operative values. One year after lobectomy, both VO_{2peak} and Wmax elicited during a CPET were 6% and 7% (respectively) lower than pre-operative values. Regarding the group that underwent pneumonectomy, decrements in VO_{2peak} and Wmax were 20% and 28%, respectively. These findings corroborate the findings of the other two studies (70, 71).

A methodological consideration consistent to all of the abovementioned studies pertains to the use of a step protocol (i.e. when work rate increments are made at intervals of one or 2 minutes), rather than a ramp protocol (i.e. when work rate increments are made continuously over shorter periods of time). Revill et al (198) reported that people with exertional dyspnoea due to COPD, asthma and sarcoidosis achieve higher Wmax during ramp protocols (110 ± 37 W *versus* 105 ± 36 W). The researchers also demonstrated that the rates of change in dyspnoea and perceived exertion each minute were 15% lower during ramp protocols (198). That is, the ramp protocol modified the perception of symptoms during maximal exercise making the CPET more acceptable for the individual (198). Although the study showed no significant differences between the two protocols for the other peak physiologic responses, the higher ramp Wmax is likely to influence exercise prescription, as a percentage of Wmax is often used to prescribe cycle training in people with lung disease including lung cancer (29, 31).

2.3.2.3.1 Limiting factor for exercise capacity following lung resection for NSCLC

Wang et al (40) demonstrated that the limiting factor for exercise capacity post-lobectomy was leg fatigue, whereas post-pneumonectomy, people felt that dyspnoea was the factor limiting their ability to exercise (40). The finding that dyspnoea is the main symptom limiting exercise after pneumonectomy could be due to the significant post-operative decrease in both breathing reserve (54% reduction) and oxygen pulse (26% reduction) reported in the same study (40). This is similar to what has been reported in people with moderate to severe COPD (199). They stop aerobic exercise mainly due to dyspnoea, because the reductions they have in breathing reserve and oxygen pulse lead to a higher ventilatory requirement to accomplish the same work compared with healthy people (199). Conversely, healthy people usually complain of leg muscle pain or general fatigue on terminating exercise (199).

Although being widely used to investigate the effects of exercise training on exercise capacity in people with respiratory conditions (19, 200) including NSCLC (28, 31, 36), field-based tests have not been frequently used to explore the impact lung resection has on exercise capacity in this population. To date, one study has demonstrated that, compared to pre-operative values, the distance achieved during the ISWT was reduced at one, 3 and 6 months after both lobectomy (reduction of 30%, 17% and 16%, respectively) and pneumonectomy (reduction of 40%, 29% and 23%, respectively) (71). Conversely, for the distance achieved during the 6MWT, Saad et al (201) showed no changes in 6MWD when measured at 6 months after lung resection (509 ± 99 m pre-operatively to 506 ± 95 m post-operatively; *p* value not reported) . Nonetheless, this might have been due to some of the characteristics of their participants. Of note, 17% of the participants included in the study by Saad et al (201) had undergone segmentectomy and 39% of their participants had metastatic carcinoma and carcinoid rather than primary NSCLC.

2.3.3 Health-related quality of life

2.3.3.1 Types of health-related quality of life questionnaires

Both disease-specific and generic HRQoL questionnaires have been used to investigate the impact lung resection has on people with NSCLC. The two most

commonly used disease-specific questionnaire are the European organisation for research and treatment of cancer (EORTC) quality of life questionnaire core 30 (QLQ-C30) with its lung cancer subscale (LC13) (202) and the functional assessment of cancer therapy – lung scale (FACT-L) (203). The most widely used generic questionnaire is the medical outcomes study short form 36 general health survey (SF-36) (204). These questionnaires are subdivided in components such as physical and mental (or emotional health). Both the EORTC QLQ-C30 and the FACT-L also have subscales for symptoms. Their reliability (Cronbach's α coefficient) ranges from 0.52 to 0.94 (202-204).

A recently published systematic review on HRQoL after lung resection in people with NSCLC demonstrated that the majority of the studies use generic questionnaires to assess HRQoL in this population (41). Of the 19 studies included in the review (the total number of participants was not reported), 11 (58%) used the SF-36 and eight (42%) used the EORTC QLQ-C30/LC13 to assess HRQoL.

2.3.3.2 Health-related quality of life and symptoms following lung resection for NSCLC

2.3.3.2.1 Immediate changes in health-related quality of life following lung resection

No studies have been published that assessed HRQoL, using the SF-36 or the FACT-L, as early as one month following lung resection. Findings of studies that used the EORTC QLQ-C30/LC13 suggest that there is a significant reduction in physical function one month following lung resection compared to pre-operative values (41, 205, 206). Conversely, the same studies (41, 205, 206) have demonstrated that emotional function one month following lung resection was similar to pre-operative values. Kenny et al (206), for instance, assessed 173 people undergoing lung resection for NSCLC using the EORTC QLQ-C30/LC13 and demonstrated a decrement of 16% (or 13 points) in physical function one month following lung resection for NSCLC. Besides being a statistically significant change, this decrement is also clinically meaningful. Using changes in the WHO performance status, which ranges from 0 (no symptoms of cancer) to 4 (bedbound), as a clinical anchor, the minimal clinically important difference (MCID) for deterioration in the physical

function subscale of the EORTC QLQ-C30/LC13 has been defined to be 4 points (207). As opposed to physical function, the same study showed that emotional function did not change one month after lung resection (mean difference [standard error] = 1.6 [2.0]; $p > 0.05$).

2.3.3.2.2 Medium term changes in health-related quality of life following lung resection

Of the 19 studies included in the previously mentioned systematic review by Poghosyan et al (41), 11 (58%) used the SF-36 and eight (42%) used the EORTC QLQ-C30/QLQ-C13 to assess HRQoL. Seven included studies that used the SF-36 followed participants for at least 6 months. Six of these seven studies reported that the physical function domain of the SF-36 demonstrated a worsening at 6 months following lung resection for NSCLC (41). For instance, a prospective population-based cohort study of 141 people showed that, compared to pre-operative score, the physical component score of the SF-36 reduced by 9 points (or 19%) at 6 months following lung resection for lung cancer ($p = 0.03$) (208). Conversely, compared to pre-operative score, the same study demonstrated a 10% (4 points) increase in the mental component score of the SF-36 at 6 months following lung resection for lung cancer ($p = 0.01$). These results are consistent with data from other studies (209, 210) and are likely to be clinically meaning as the MCID for the components of the SF-36 ranges from 3 to 5 points (211). The improvement in the mental component score is likely to be due to the fact that people with NSCLC are aware that lung resection has the potential to prolong their lives or even offer them a chance of a cure (103).

In studies that used the EORTC QLQ-C30/LC13 results of physical function were less consistent than studies that used the SF-36 (41). Some researchers used the EORTC QLQ-C30/LC13 and have reported that physical functioning returned to pre-operative levels 6 months following lung resection (212, 213), whereas others reported no improvement in physical functioning over the same period of time (205, 214) or a persistent reduction in physical functioning up to 2 years after surgery (206). Methodological differences such as the inclusion of people receiving adjuvant chemotherapy, the specific surgical techniques used as well as both the type of in-

patient care and the management following discharge may have influenced these results.

Similar to the findings from studies that used the SF-36, studies that used EORTC QLQ-C30/LC13 have demonstrated improvements in the mental and/or emotional health of people following lung resection for NSCLC (206, 215). Four months following lung resection a 7% improvement in emotional health has been reported by people with NSCLC (206). Studies comparing results from different disease-specific HRQoL questionnaires with the aim of determining which questionnaire was the most responsive in people undergoing lung resection for NSCLC are needed. Further, generic HRQoL questionnaires should be used as complementary tools to disease-specific HRQoL questionnaires in people undergoing lung resection for NSCLC. They allow for comparisons across different disease-populations and also for comparisons with healthy people.

2.3.3.2.3 Symptoms following lung resection

Pain, fatigue and dyspnoea are common in people following lung resection for NSCLC (41). On discharge from hospital following lung resection for NSCLC, scores for pain, fatigue and dyspnoea were 366%, 198% and 108% worse, respectively, compared with pre-operative scores (206). Four months after discharge, symptom scores have been shown to be between 38 to 74% higher than pre-operative values (206). Approximately 50% of people who undergo surgery and are apparently disease free 2 years following the operation, continue to experience dyspnoea and fatigue (206).

2.3.4 Physical activity and sedentary behaviour

Physical activity is defined as "*any bodily movement produced by skeletal muscles that results in energy expenditure above resting (basal) levels*" (54, 216). It encompasses sports, exercise, and physical activities done as part of daily living, occupation, leisure, and transportation. Physical activity is often classified as light, moderate or vigorous intensity, according to the level of energy expenditure required (49). For example, light intensity physical activity involves energy expenditure > 1.5 and ≤ 3 metabolic equivalent units (METs). One MET is the energy cost of resting

quietly, often defined in terms of oxygen uptake as 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$. Light intensity physical activity would include activities such as slow walking, washing dishes and showering and ironing in standing. Moderate intensity physical activity involves energy expenditure > 3 and ≤ 6 METs. It would include brisk walking, dancing and jogging. Finally, vigorous intensity physical activity would include activities such as running, cycling, walking uphill at a fast pace and competitive sports such as rowing and swimming, which involve an energy expenditure > 6 METs (49, 60).

Behaviours characterised by low energy expenditure (< 1.5 METs) are considered sedentary behaviours (60). Such behaviours can also be part of the assessment of physical activity. Sedentary behaviour is defined both by low energy expenditure and a sitting or reclining posture (61). They occur throughout waking hours (i.e. sleep is not considered a sedentary behaviour), and across work, leisure, domestic, and transport domains. Common behaviours that occur while sedentary include television viewing, reading, driving and computer use.

The importance of subdividing waking time according to intensity is supported by research showing that (i) time spent in moderate-to-vigorous physical activity is correlated with functional exercise capacity (65) and it is an independent predictor of mortality in people with chronic lung disease (57); (ii) low physical activity level is a predictor of respiratory-related exacerbations in people with moderate to severe COPD (57, 58); (iii) light-intensity physical activity may reduce the risk of developing type-2 diabetes and cardiovascular diseases in healthy adults (48) and (iv) sedentary behaviour is a risk factor for metabolic diseases, independent of the level of physical activity, in the general population (47).

Physical activity and sedentary behaviour can be measured both subjectively (e.g. self-reported questionnaires) and objectively (physical activity monitors such as pedometers, accelerometers and metabolic monitors).

2.3.4.1 Questionnaires to quantify physical activity

Physical activity questionnaires are inexpensive and easy to apply, however they depend on accurate perception and recall of information by the respondents (217). The ones with better-documented validation in elderly are the Minnesota leisure time

physical activity questionnaire (MLTPAQ) (218), the Baecke questionnaire (219) and the physical activity scale for the elderly (PASE) questionnaire (220). For the latter (220) people have to recall time spent (in hours per day) in activities of different intensities performed during the past week. The other two questionnaires (218, 219), require people to recall activities performed in the past year. Evidence pertaining to reliability, validity and responsiveness of these few instruments in people following lung resection for lung cancer is lacking.

Although data obtained via subjective measures, such as questionnaires, may lack precision due to the long recall period (221), detailed questioning over recent time periods (i.e. 2 days) has been shown to improve the reliability of the data obtained in people with moderate to severe COPD (222). The MARCA (Multimedia Activity Recall for Children and Adults) (222) has demonstrated intra-class correlation coefficients for test-retest reliability ranging from 0.86 to 0.99. It has also been validated against two physical activity monitors, in people with moderate to severe COPD, for capturing time and energy expenditure associated with physical activities and sedentary behaviours (222).

One of the advantages of subjective measures is that they offer the opportunity to obtain detailed information regarding type of activities undertaken during daily life. This allows clinicians to establish targets and goals pertaining to participation in physical activities, based on individual preferences. The low cost associated with self-report measures of physical activity has resulted in their widespread use in clinical practice and epidemiological research.

2.3.4.2 Physical activity monitors

Pedometers, accelerometers and metabolic monitors have been widely used to measure physical activity. The measurement properties of these devices and their output vary considerably. Most devices require technical expertise to collect, download and interpret the data. When choosing a physical activity monitor, reliability, validity, responsiveness and cost as well as study objectives and characteristics of the population need to be considered (223).

Beyond the selection of an activity monitor, and the appropriate outcome, two steps must be undertaken to minimise variability in physical activity: ensuring sufficient and comparable hours of assessment and ensuring sufficient number of valid days of assessment. Hours per day and number of days and of activity monitoring should not be overly burdensome for the participants but should be sufficiently long to reflect their habitual level of activity (224). Values of 10 h or 60% of waking hours have been proposed as a valid day (225). Estimates of 3 to 7 valid days (224, 225) have been reported as acceptable, with 2 valid days of measurement considered as the minimum number of necessary days to assess physical activity in people with low levels of physical activity such as people with moderate to severe COPD (intra-class correlation coefficient [ICC] ≥ 0.7) (65). To date, there is still no firm consensus on what is the minimum number of days and hours per day of activity monitoring needed to reliably predict physical activity and sedentary behaviour in people following lung resection for lung cancer.

In middle-aged adults (38 ± 10 yrs), it has been suggested that 5 consecutive days of activity monitoring using a pedometer are enough (ICC ≥ 0.8) to predict one year of daily steps (226). Pertaining to accelerometery, 3 to 4 valid days of monitoring have been suggested to reliably predict physical activity (depending on the monitor of choice) (226).

2.3.4.2.1 Pedometers

Pedometers or 'step counters', the simplest physical activity monitors, are small and inexpensive instruments. They are usually worn on the waist and provide information on vertical movement by recording the number of times the horizontal spring-suspended lever arm within the pedometer deflects with vertical acceleration. Therefore, one of the errors of pedometers is that any vertical movement (e.g. standing up from a chair) will be count as a step. In addition to this limitation, pedometers provide no information about pattern of physical activity and sedentary behaviour or the intensity at which activities are performed. Further, they have been consistently demonstrated to underestimate steps during slow-walking speeds (227-229) and in obese people (5% to 18% underestimation depending on walking speed) (230).

Despite their limitations, pedometers have been shown to be useful tools in public health campaigns aiming to promote physical activity (231) and in studies focusing on increasing physical activity levels of specific populations. Zabatiero et al (232) reported a 45% increase in steps per day in physically inactive smokers after they wore a pedometer for 4 months and were encouraged to accumulate 10,000 steps per day. Studies that used a pedometer as a motivational tool for increasing physical activity in people with acute coronary syndrome and type 2 diabetes have demonstrated similar results (233, 234).

The Stepwatch activity monitor (SAM) (Cyma Corp., Seattle, WA, USA) has been proposed as a step counter that goes beyond the scope of a pedometer. It is a small (75 × 50 × 20 mm), lightweight (38 g) microprocessor-controlled motion sensor worn on the right ankle which responds to time, acceleration and position. It not only counts steps, but also provides a profile of walking activity. The SAM has a sampling frequency of 128 Hz and data are available in one-minute epochs. In people with COPD, this motion sensor has been shown to be accurate in detecting step rate (compared to direct observation) regardless of walking speed or use of a walking aid (wheeled-walker) (235). The mean difference (MD) between the step rate derived using the SAM and direct observation has been reported to be 2 steps·min^{-1} (with a limit of agreement of 6 steps·min^{-1}) (235).

2.3.4.2.2 Accelerometers and metabolic monitors

Over recent years, interest has emerged in capturing not only steps or body movement but also the type of activity performed. With the advance of technology in this field, several accelerometers and metabolic monitors have been created with the aim of determining quantity and intensity of movement during a specific period of time (236). Several monitors can be used to subdivide waking time into sedentary behaviour, light, moderate and vigorous intensity physical activity. They are mostly used in research, however as technology in this area is advancing quickly, it is likely that the collection of robust physical activity data via accelerometers and metabolic monitors will be feasible for clinicians in the near future.

One of the most widely utilised physical activity monitors in the field of respiratory diseases is the SenseWear armband (SAB) (BodyMedia, Inc., Pittsburgh, PA, USA). The newest model of the SAB (the MF-SW) is a small (55mm × 62mm × 13mm) and light (45g) portable metabolic monitor which has been validated to estimate energy expenditure in people with chronic lung diseases as well as in other populations (229, 237-239). The device is worn over the triceps brachii muscle bulk of the left arm and, in addition to its tri-axial accelerometer, it is also fitted with three other sensors which detect: (i) heat flux; (ii) skin temperature and; (iii) galvanic skin response. Hill et al (237) assessed stationary and active tasks in people with moderate-to-severe COPD and demonstrated that the difference between the energy expenditure (considering all tasks together) estimated by the SAB and indirect calorimetry was -0.2 METs (p=0.21), with a limit of agreement of 1.3 METs. In keeping with this finding, another study that assessed five different daily activities also in people with moderate-to-severe COPD has shown no significant differences between energy expenditure estimated by the SAB compared to indirect calorimetry for the sum of the five activities (SAB energy expenditure = 22.7 ± 7 kcal *versus* indirect calorimetry energy expenditure = 21 ± 8 kcal; $p > 0.05$) (229).

Due to their accuracy, the StepWatch and the SAB are the monitors that will be used in the studies described in this PhD thesis.

2.3.4.3 Physical activity and sedentary behaviour following lung resection for NSCLC

In people undergoing treatment for stages I to IIIB NSCLC, results from a study that assessed physical activity both subjectively and objectively over a period of 6 months demonstrated differences between self-reported and objectively-measured physical activity (240). People with NSCLC were assessed at three time-points: (i) the time of diagnosis (baseline); (ii) 10 weeks following diagnosis and (iii) 6 months following diagnosis. Forty-seven percent (23 of 49 participants) of those included did not undergo lung resection. Physical activity was assessed subjectively by the PASE and objectively (number of daily steps) using a tri-axial accelerometer. For the PASE, data from the 47 participants were included in the final analysis, whereas accelerometry data of only 28 participants were included in the final analysis. Data

from the tri-axial accelerometer showed no changes in daily steps across the three time-points (mean and standard error [SE] = 6182 [549] steps/day at baseline; 5818 [628] steps/day 10 weeks following diagnosis and 6171 [524] steps/day 6 months following diagnosis). However, at 10 weeks and 6 months following diagnosis the PASE score was 34% and 24%, respectively, lower than the baseline score indicating less activity (240). The difference in proportion of participants who had their subjective and objective data analysed may have influenced the results. Importantly, the outcome measure of the objective assessment of physical activity was daily steps rather than time spent in different activity intensities. As the questions of the PASE are not limited to daily walking activities, it is likely that the PASE provided important information about changes in patterns of physical activity and sedentary behaviour that were not detected by daily steps.

Literature specific to the impact of lung resection for NSCLC on physical activity is somewhat scarce. Also, no studies have been published that investigated patterns of sedentary behaviour in this population. Studies using devices such as accelerometers and metabolic monitors are yet to be published. To date, only one study has been published that investigated changes in physical activity specifically following lung resection for NSCLC (241). Physical activity outcome, however, was limited to daily steps. The study used a pedometer (OMROM Walking Style Pro) to assess physical activity (number of daily steps) of people with NSCLC before and after lung resection. Prior to surgery, participants wore the pedometer from the initial consultation to hospital admission. Following lung resection, participants wore the pedometer for 30 days following discharge. This prospective study of 21 people who underwent either lobectomy (n = 18) or pneumonectomy (n = 3) for NSCLC, demonstrated that the mean daily steps performed during the 30 days after discharge decreased 25% relative to pre-operative values in the lobectomy group (10,703 ± 3807 steps/day pre-operatively *versus* 7978 ± 4486 steps/day post-operatively) and by 49% (4809 ± 828 steps/day pre-operatively *versus* 2491 ± 886 steps/day post-operatively) in the pneumonectomy group (241). Importantly, the abovementioned study did not report the patterns of physical activity and sedentary behaviour of the participants. Also, the researchers did not compare their participants with age and gender-matched healthy people. Nevertheless, the study provided data that made

simple comparisons with both people with advanced NSCLC and people with other lung diseases possible. For example, post-operatively, the number of daily steps of the lobectomy group (7978 ± 4486 steps per day) was almost twice as high as that reported in people with advanced stage NSCLC (4,246 ± 2,983 steps per day) (242) and similar to the number of daily steps reported in people with mild COPD (7,960 ± 3,421) (243). Although data from the pneumonectomy group should be considered with caution due to the very small sample of three participants, their number of daily steps performed post-operatively (2491 ± 886 steps/day) was almost half the number of daily steps of people with advanced stage NSCLC (242) and comparable to that reported in people with very severe COPD (2,796 ± 1,916) (243).

There is still a lack of information on patterns of physical activity and sedentary behaviour in people following lung resection for NSCLC. Further studies, using more sophisticated physical activity monitors are warranted. Comparisons with age and gender-matched healthy people are also needed in order to advance knowledge in this field.

2.3.5 Muscle force

People with cancer generally present with muscle weakness as a result of skeletal muscle wasting (loss of muscle mass) (244). Cancer-related muscle wasting has been attributed to various mechanisms, such as a hyper-metabolic status, caused by a direct effect of the tumour-induced secretion of hormones or cytokines in the organism and cancer-related fatigue, caused mainly by the cancer-treatment (245).

Specifically, in people with advanced lung cancer, muscle force via hand dynamometry (handgrip) has been investigated and shown to be decreased in 22% compared to their healthy contemporaries (246). However, data pertaining to muscle force in people following lung resection for early stage NSCLC is scant. Only one study compared muscle force before and after lung resection for NSCLC. Arbane et al (36) assessed quadriceps force via magnetic stimulation of the femoral nerve, an effort-independent technique, in 16 people with NSCLC at three time points; (i) before surgery, (ii) 5 days following lung resection and, (iii) 12 weeks following lung resection. The study showed a significant decrement in quadriceps force when

compared with pre-operative values (29.1 ± 10.9 kg) to 5 days following lung resection (21.5 ± 7.7 kg) ($p < 0.05$) followed by an improvement at 12 weeks following lung resection (26.4 ± 9.7 kg) to values close to pre-operative measures (36). One limitation of this study was that values were not compared to measures obtained in a healthy sample or with normative data. The effect lung resection has on handgrip force has not yet been investigated in this population.

2.3.6 Feelings of anxiety and depression

Feelings of anxiety and depression are commonly experienced by people with NSCLC before lung resection. They fear the surgery and are concerned about death, loss of function, deformity and pain (247). Before hospital discharge following lung resection, feelings of anxiety and depression have been demonstrated to be significantly improved by 15 and 10%, respectively (247) compared to pre-operative values. In those people who survive 22 months after the lung resection, feelings of anxiety and depression seem to be even more improved. Myrdal et al (18), assessed 112 people after lung resection for lung cancer (average of 22 ± 12 months) using the hospital anxiety and depression scale (HADS) and demonstrated that the majority of them (75%) did not have scores that represented clinical anxiety or depression. The average scores for symptoms of anxiety and depression were 5.0 and 3.8, respectively (standard deviation not reported; values > 7 are considered borderline abnormal and values > 11 are considered abnormal). Studies assessing feelings of anxiety and depression during the initial months after discharge are yet to be published.

Part 4

2.4 The role of physiotherapy and exercise training following lung resection for NSCLC

This part explores the role of physiotherapy and exercise training following lung resection for NSCLC. An extension of this part is presented in Chapter 3, which is a Cochrane systematic review on exercise training following surgery for NSCLC undertaken as part of this doctoral programme of research. The protocol of this review was published in *The Cochrane Library in 2012* (104). The full version of the review was published in *The Cochrane Library in 2013* (105). This review was co-published in 2014 in Cancer Treatment Reviews (106).

2.4.1 Physiotherapy for people following lung resection for non-small cell lung cancer

Reeve et al (37) conducted a survey and described the physiotherapy management of patients (not only people with lung cancer) undergoing thoracotomy in 2007. The study reported that in 96% of hospitals included in the analysis (44 of 46 hospitals), people undergoing thoracotomy were seen by a physiotherapist following surgery. Of note, whether this level of intervention is necessary in this patient group still remains to be determined.

A randomised controlled trial (RCT) conducted in New Zealand (34) examined the effects of physiotherapy on the incidence of pulmonary complications (e.g. pneumonia), intensive care unit re-admissions and length of hospital stay, in people following lung resection (not only people with lung cancer). Physiotherapy techniques included breathing exercises, ambulation and a progressive shoulder and thoracic cage mobility programme (34). This study failed to demonstrate between-group differences (i.e. treatment *versus* control) on the three outcomes analyses. This result was likely to be due, at least in part, to an overall rate of post-operative pulmonary complications of less than 4% (3 out of 76 people). It is likely that such interventions are most appropriate for those who develop a post-operative pulmonary complication or have limited capacity to participate in early mobilisation.

Data on physiotherapy management of specifically people following lung resection for NSCLC is presented in Chapter 4, which is a survey reporting current physiotherapy practice patterns across hospitals in Australia and New Zealand for people who require surgical resection for lung cancer undertaken as part of this doctoral programme of research. The survey was published in 2013 (248).

2.4.2 Exercise training for people following lung resection for non-small cell lung cancer – results from single-group studies

Several single-group studies have been published that investigated the role of exercise training for people diagnosed with early stage NSCLC (28-31, 249-252). However, most of these studies included both people who underwent lung resection (with or without adjuvant chemotherapy) and people who only had chemo/radiotherapy and did not undergo lung resection (30, 249-252). This broad inclusion criterion precludes the establishment of the role of exercise training in people with different stages of NSCLC. Therefore, the results of these studies do not address the role of exercise training specifically in people following lung resection for NSCLC.

Only three published studies have investigated the effect of exercise training for people with NSCLC who underwent lung resection (with or without adjuvant chemotherapy) (28, 29, 31). They were all prospective studies that had cycling as the main component of their supervised exercise training programme. Jones et al (29) did not mention how long after lung resection the exercise training programme was initiated. Spruit et al (31) reported that their participants were recruited from the outpatient clinic at a median of 3 [2.5 to 9.3] months after completing intensive lung cancer treatment. Cesario et al (28) started their in-patient exercise programme on day one after lung resection (Table 2-2).

Table 2-2: Description of exercise training programmes

Study	Type of exercise	Intensity	Duration (minutes)	Frequency (per week)	Length (weeks)
Spruit et al (31) n =10	Cycling Treadmill Weights (upper and lower limbs)	60% of maximum work rate 80% of average walking speed (6MWT) 60% of 1 repetitium maximum	20 20 30	Daily	8
Cesario et al (28) n = 25	Cycling	70—80% of maximum work rate	30	Daily	4
Jones et al (29) n = 19	Cycling	60 to 70% of maximum work rate	15 to 45	3 times	14

2.4.2.1 Characteristics of the participants

All the participants included in the three studies had undergone lung resection for NSCLC. Age and body-mass index (BMI) of the participants were 65 [59 to 70] years and 24 [21 to 28] $kg \cdot m^{-2}$ in the study by Spruit et al (31) and 62 ± 11 years and 26 ± 8 $kg \cdot m^{-2}$ in the study by Jones et al (29). Cesario et al (28) did not report age or BMI of their participants. Pertaining to the type of lung resection, the study by Spruit et al (31) included five participants following lobectomy, one following bi-lobectomy and four following pneumonectomy. Cesario et al (28) did not report type of lung resection and Jones et al (29) included 12 participants following lobectomy, one following bi-lobectomy, one following pneumonectomy, one following wedge resection and the type of surgical procedure was not reported in four participants. Four (40%) participants in the study by Spruit et al (31) and eight (42%) participants in the study by Jones et al (29) received adjuvant treatment.

2.4.2.2 Outcomes

Regarding outcomes, exercise capacity was the main outcome of all three studies. Spruit et al (31) reported 6MWD as well as Wmax as outcome measures, Cesario et al (28) reported 6MWD and Jones et al (29) reported VO_{2peak} and Wmax collected during a CPET. Lung function was also assessed in two studies (28, 31) and HRQoL (FACT-L) was assessed in one study (29).

2.4.2.3 Change in outcome measures following exercise training

All three studies reported improvements in exercise capacity following exercise training (Table 2-3). Specifically, improvements were demonstrated in 6MWD (28, 31) and Wmax (29). Improvements in VO_{2peak} were demonstrated only in those that did not receive adjuvant chemotherapy (baseline 15 ± 3 $ml \cdot kg^{-1} \cdot min^{-1}$; following exercise training 16.7 ± 4 $ml \cdot kg^{-1} \cdot min^{-1}$; mean change 1.7 [0.6 to 3] $ml \cdot kg^{-1} \cdot min^{-1}$; $p = 0.008$) (29). Jones et al (29) also reported better results on the FACT-L subscales functional well-being and fatigue following exercise training (Table 2-3). No changes in lung function following exercise training were seen.

Table 2-3: Change in exercise capacity and HRQoL following exercise training

Study	Outcome measures	Value at baseline	Value following exercise training	Mean difference [95% CI]	*p value*
Spruit et al (31)	6MWD (m)	351 [240 to 436][a]	Not reported	145 [65 to 245]	*0.002**
n =10	Wmax (W)	82 [54.5 to 91][a]	Not reported	26 [16 to 39]	*0.008**
Cesario et al (28) n = 25	6MWD (m)	298 (SD not reported)	393 (SD not reported)	Not reported	*0.01**
Jones et al (29)	VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	15.7 ± 3.3[b]	16.8 ± 3.9	1.1 [-0.3 to 2.5]	*0.11*
	Wmax (W)	74± 9[b]	83 ± 22	9 [3 to 14]	*0.003**
n = 19	FACT-L FWB†	17 ± 5[b]	20 ± 5	4 [1 to 6]	*0.007**
	FACT-L fatigue$^{\mp}$	19 ± 8[b]	12 ± 8	-7 [-1 to -17]	*0.03**

Abbreviations: 6MWD: six-minute walk distance; CI: confidence interval; FACT-L: Functional assessment of cancer therapy – lung scale; FWB: functional well-being; SD – Standard deviation; VO_{2peak}: peak rate of oxygen uptake; Wmax: maximum work rate. [a] median [interquartile range]; [b] mean ± and standard deviation; † Higher scores indicate an improvement; $^{\mp}$ Lower scores indicate an improvement.
**Statistically significant difference; $p < 0.05$.*

2.4.2.4 Discussion of results

These three single-group studies showed that exercise training is safe, feasible, well tolerated and may confer benefit for people following resection for lung cancer. No adverse effects of exercise training were reported in any of the studies. Jones et al (29) reported that adherence to the exercise training programme was 85%, which seems to be higher than that reported in people with advanced NSCLC (44 to 73%) (253, 254). Exercise training may also have a role in increasing exercise capacity and some components of HRQoL following lung resection for NSCLC, especially amongst people not receiving adjuvant chemo/radiotherapy. However, these three studies recommended that large RCTs are needed to provide more conclusive evidence regarding the role of exercise training in this population.

Additional considerations

Larger studies, with a much more rigorous methodology are needed. From the inclusion criteria to the way data are shown and results are presented. Further, inclusion of all types of lung resection may not be the most appropriate choice. As discussed before, the impact pneumonectomy has on both lung function and exercise capacity is greater than the impact lobectomy has on the same outcomes. This is likely to influence exercise prescription, monitoring and goals during exercise training. Therefore, it can be speculated that responses to exercise training have the potential to differ from people who underwent lobectomy to people who underwent pneumonectomy. Results from RCTs are discussed in the upcoming section.

2.5 Summary

Lung cancer is an important problem worldwide and the most common type of lung cancer is NSCLC. People in early stage NSCLC (i.e. stages I, II and IIIA) are considered eligible surgical resection of the tumour however, although surgical resection offers them a chance of cure, it negatively impacts lung function, maximal exercise capacity and symptoms such as dyspnoea and fatigue (68-71, 189, 190). Regarding quality of life, significant reduction in physical function rather than emotional function have also been demonstrated following lung resection (41, 205, 206). The impact lung resection for NSCLC has on other important outcomes such as

patterns of physical activity and sedentary behaviour, muscle force and feelings of anxiety and depression is still uncertain.

Exercise training has been demonstrated to be safe, feasible and well tolerated by people following resection for lung cancer (28, 29, 31). Exercise training may also have a role in increasing exercise capacity (28, 29, 31) and HRQoL (29) of this population, however larger studies, with more rigorous methodology are needed in order to confirm these findings and to investigate other possible benefits that exercise training is likely to provide.

CHAPTER 3

COCHRANE SYSTEMATIC REVIEW

Overview

This Chapter pertains to a Cochrane systematic review on exercise training following surgery for non-small cell lung cancer (NSCLC) undertaken as part of this doctoral programme of research. The primary aim of this systematic review was to determine the effects of exercise training on exercise capacity in people following lung resection (with or without chemotherapy) for NSCLC. The secondary aims were to determine the effects of exercise training on other outcomes such as health-related quality of life (HRQoL), lung function, peripheral muscle force, dyspnoea and fatigue as well as feelings of anxiety and depression. The protocol of this review was published in *The Cochrane Library in 2012* (104). The full version of the review was published in *The Cochrane Library in 2013* (105) and the review was co-published in 2014 in Cancer Treatment Reviews (106).

The specific question answered in this Chapter is: What is the current evidence for exercise training in people following lobectomy for NSCLC?

3.1 Methods

3.1.1 Types of studies

This review included randomised controlled trials (RCTs) in which the study participants were allocated to receive either exercise training or no exercise training following lung resection for NSCLC. Studies and abstracts published in any language were eligible for inclusion.

3.1.2 Types of participants

Inclusion criteria comprised participants following lung resection for NSCLC, performed via video-assisted thoracoscopic surgery (VATS) or thoracotomy, with or without induction or adjuvant chemotherapy. Study participants who had undergone lung resection via either approach were included because earlier work (255) has demonstrated that important outcomes such as short-term mortality, length of hospital stay and hospitalisation costs were similar between these groups. This is despite the fact that people who undergo resection via VATS or thoracotomy differ in terms of pain and shoulder dysfunction (256). Participants who had undergone resections of any type (i.e. wedge resection, segmentectomy, lobectomy or pneumonectomy) were eligible for inclusion. However, study participants were excluded if they had received treatment that aimed only at palliation following diagnosis or had an anticipated survival following diagnosis of less than 12 months. People with small cell lung cancer (SCLC) were excluded from this review because metastasis is common at the time of diagnosis and the median survival is usually less than 12 months.

3.1.3 Types of interventions

The intervention comprised exercise training of any type (aerobic exercise, resistance exercise, respiratory muscle training or any combination) initiated within 12 months following lung resection. Training sessions could be supervised or unsupervised, or a combination of both. Characteristics of the training programme, such as intensity, frequency, duration, type, adherence and extent of supervision, were recorded where possible. Any adverse events were also documented. Control groups received usual care with either no exercise training or only instructions pertaining to exercise training.

3.1.4 Primary outcomes

The primary outcome was any measure of exercise capacity including peak rate of oxygen consumption (VO_{2peak}) and the six-minute walk distance (6MWD).

3.1.5 Secondary outcomes

1. HRQoL (e.g. the medical outcomes study short form 36 general health survey (SF-36), the European organisation for research and treatment of cancer quality of life questionnaire core 30 (EORTC QLQ-C30) and the St. George's respiratory questionnaire (SGRQ)).

2. Force-generating capacity of peripheral muscles (e.g. measures of upper and lower limbs muscle strength).

3. Pressure-generating capacity of respiratory muscles (e.g. maximal inspiratory and expiratory pressures).

4. Dyspnoea (e.g. the BORG category ratio scale) or functional limitation during daily life resulting from dyspnoea (e.g. the medical research council dyspnoea scale).

5. Fatigue (e.g. the functional assessment of chronic illness therapy - fatigue subscale).

6. Feelings of anxiety and depression (e.g. the hospital anxiety and depression scale).

7. Lung function (e.g. volumes, flows and diffusing capacity).

8. Mortality.

9. Development of a post-operative pulmonary complication (only for studies that initiated the exercise training programme prior to discharge from hospital following surgery).

3.1.6 Search methods for identification of studies (electronic searches)

Trials were identified using electronic bibliographic databases including:

1. the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, issue 2 of 12);

2. MEDLINE (via PubMed) (1966 to February 2013);

3. EMBASE (via Ovid) (1974 February 2013);

4. SciELO (The Scientific Electronic Library Online) (1978 to February 2013);

5. PEDro (Physiotherapy Evidence Database) (1980 to February 2013).

The search strategies that were used for MEDLINE and CENTRAL are presented in Appendix 1 and Appendix 2, respectively. The strategy was adapted for use in the other databases.

Abstracts from scientific meetings of the American Thoracic Society, the European Respiratory Society and the Thoracic Society of Australia and New Zealand (2002 to February 2013) were also handsearched.

3.1.7 Searching other resources

Reference lists of all primary studies and review articles were screened for additional references. Authors of identified trials were contacted and asked to identify further published and unpublished studies.

3.1.8 Data collection and analyses

3.1.8.1 Selection of studies

Two review authors (Vinicius Cavalheri [VC] and Fatim Tahirah [FT]) independently examined the titles and abstracts of all studies identified using the search strategy to determine eligibility for inclusion. Decisions of the two review authors were recorded and disagreements were resolved by discussion.

3.1.8.2 Data extraction and management

Two review authors (VC and FT) extracted data using a standardised form. Disagreements were resolved by discussion, or where necessary, by a third review author (Kylie Hill [KH]). Once consensus was reached, data were entered into the software (the Review Manager 5.1 [RevMan 5.1]) by the first review author (VC). Data included details of the studies, characteristics of the participants and the results.

Where applicable, the authors of the included studies were asked to verify and provide details of missing data.

3.1.8.3 Assessment of risk of bias in included studies

Risk of bias for included studies was assessed as high, low or unclear, with the last category indicating either a lack of information or uncertainty regarding the potential for bias. The Cochrane Collaboration's 'seven evidence-based domains' tables (random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and other possible sources of bias) was used. Disagreements were resolved by discussion or, where necessary, by a third review author (KH). Study authors were contacted to seek clarification on issues pertaining to bias.

3.1.8.4 Measures of treatment effect

No dichotomous outcomes have been included in the analysis. The mean difference (MD) and standardised mean difference (SMD) together with their corresponding 95% confidence intervals (CIs) were calculated for continuous outcomes. The MD was calculated for exercise capacity (6MWD) and lung function (forced expiratory volume in one second [FEV_1]). The SMD was calculated for HRQoL, as this outcome was measured using questionnaires with different scale directions. For the SF-36 and the EORTC QLQ-C30, higher scores indicate less limitation whereas for the SGRQ higher scores indicate more limitation. In order to pool these data, the mean scores of the SGRQ were subtracted from the maximum possible value for its scale (one hundred (100)). Therefore, in this review, higher scores for HRQoL indicate less limitation.

3.1.8.5 Dealing with missing data

The authors of all included studies were contacted to obtain missing data.

3.1.8.6 Assessment of heterogeneity

Heterogeneity and the extent of inconsistency between studies were assessed by visual inspection of the forest plots, the Chi^2 test and using the I^2 statistic.

3.1.8.7 Assessment of reporting biases

In order to reduce publication bias, a comprehensive literature search was conducted, that encompassed published and unpublished studies as well as trial registries. As the number of studies included in this review was less than 10, funnel plots were not generated.

3.1.8.8 Data synthesis

The RevMan 5.1 was used to conduct the statistical analyses and generate forest plots. Initially, a random-effects model was used for calculating summary estimates. As the studies were found to be homogeneous, a fixed-effect model was applied. The results of homogeneous studies were meta-analysed using the inverse variance DerSimonian and Laird method (257). Where data aggregation was not possible, a narrative discussion of the study results was undertaken.

A GRADE 'Summary of findings' table (258, 259) was created in order to interpret findings. This was achieved by exporting data from RevMan 5.1, preparing the table, and importing it back into RevMan 5.1. The outcomes that were included in the 'Summary of findings' table were (i) 6MWD; (ii) HRQoL (SF-36, EORTC QLQ-C30 or the SGRQ) and (iii) lung function (FEV_1). Outcomes expressed as numerical data were edited using the 'summary of findings' screen. The quality of evidence for each outcome was assessed by downgrading or upgrading evidence in accordance with the GRADE criteria. Assumed risk for these outcomes was calculated using the post-intervention values across control groups. The corresponding risk (and 95% CI) for these outcomes was expressed as the MD or SMD of the post-intervention values measured in the intervention group minus the assumed risk.

3.2 Results

3.2.1 Description of studies

For complete details of studies which were classified as included or excluded, see Table 3-1 (characteristics of included studies) and Appendix 3 (characteristics of excluded studies).

Table 3-1: Characteristics of included studies

Studies	**Arbane 2011**	**Brocki 2010**	**Stigt 2013**
Methods	Randomised controlled trial Study duration: Five days (in-patient) + 12 weeks of home-based intervention. Assessments were performed pre-operatively, 5 days post-operatively and after the 12 weeks of intervention.	Randomised controlled trial Study duration: Three months of intervention. Assessments were performed before and after intervention period.	Randomised controlled trial Study duration: 12 weeks of intervention and one-year follow-up. Assessments were performed before surgery and post-operatively at one, 3, 6 and 12 months.
Participants	51 participants (median [range] age 63 [32 to 87] yr [CG]; 65 [47 to 82] yr [EG]) following lung resection for NSCLC completed the study.	78 participants (mean ± SD age 65 ± 9 yr [CG]; 64 ± 10 yr [EG]) following lung resection for NSCLC were included.	81 participants (mean ± SD 63 ± 10 yr [CG]; 64 ± 10 yr [EG]) following open thoracotomy for NSCLC were invited. Sixty participants accepted but 57 were randomised before surgery. Forty-nine participants completed the study.
Intervention	CG (n = 25): Usual Care EG (n =26): Twice daily strength and mobility training from day one to day 5 post-surgery as well as 12 weeks of home-based non-supervised exercise programme (walking + home-adapted strengthening exercises) including three home visits.	CG (n = 37): Usual care EG (n = 41): Aerobic exercise, resistance training and dyspnoea management. Target intensity was set at 60% to 80% of participant's peak work rate. Exercise programme initiated following the assessments which took place 3 weeks after discharge.	CG (n = 26): Usual care EG (n = 23): Four weeks after discharge, twice a week, participants exercised at 60-80% of their peak work rate and performed muscle training for 12 weeks.
Outcomes	Exercise capacity (6MWD), health-related quality of life (EORTC QLQ-C30) and maximal quadriceps force (femoral nerve stimulation).	Exercise capacity (6MWD), health-related quality of life (SF-36) and lung function (spirometry).	Exercise capacity (6MWD), health-related quality of life (SGRQ and SF-36), and pulmonary function (spirometry).

Abbreviations: 6MWD: six-minute walk distance; CG – Control group; EG – Exercise group; EORTC QLQ-C30 - European organisation for research and treatment of cancer quality of life questionnaire core 30; NSCLC – Non-small cell lung cancer; SF-36 - Medical outcomes study short form 36 general health survey ; SGRQ - St. George's respiratory questionnaire; VATS – Video-assisted thoracoscopic surgery.

3.2.2 Results of the search

The search of all the databases in February 2013 yielded a total of 459 records: 73 from CENTRAL; 297 from MEDLINE; 76 from EMBASE; 10 from PEDro and three from ScIELO. After removing duplicates the total was 399. Based on title and abstract 362 were excluded leaving 37 full texts and conference abstracts to be assessed for eligibility. Thirty-four studies were excluded as they either did not meet review criteria (n = 31), were conference abstracts of included studies (n = 2) or the authors did not reply to several contact attempts (n = 1) (Figure 3-1). The authors of the three studies eligible for this review (two full texts and one conference abstract) were contacted to obtain missing data.

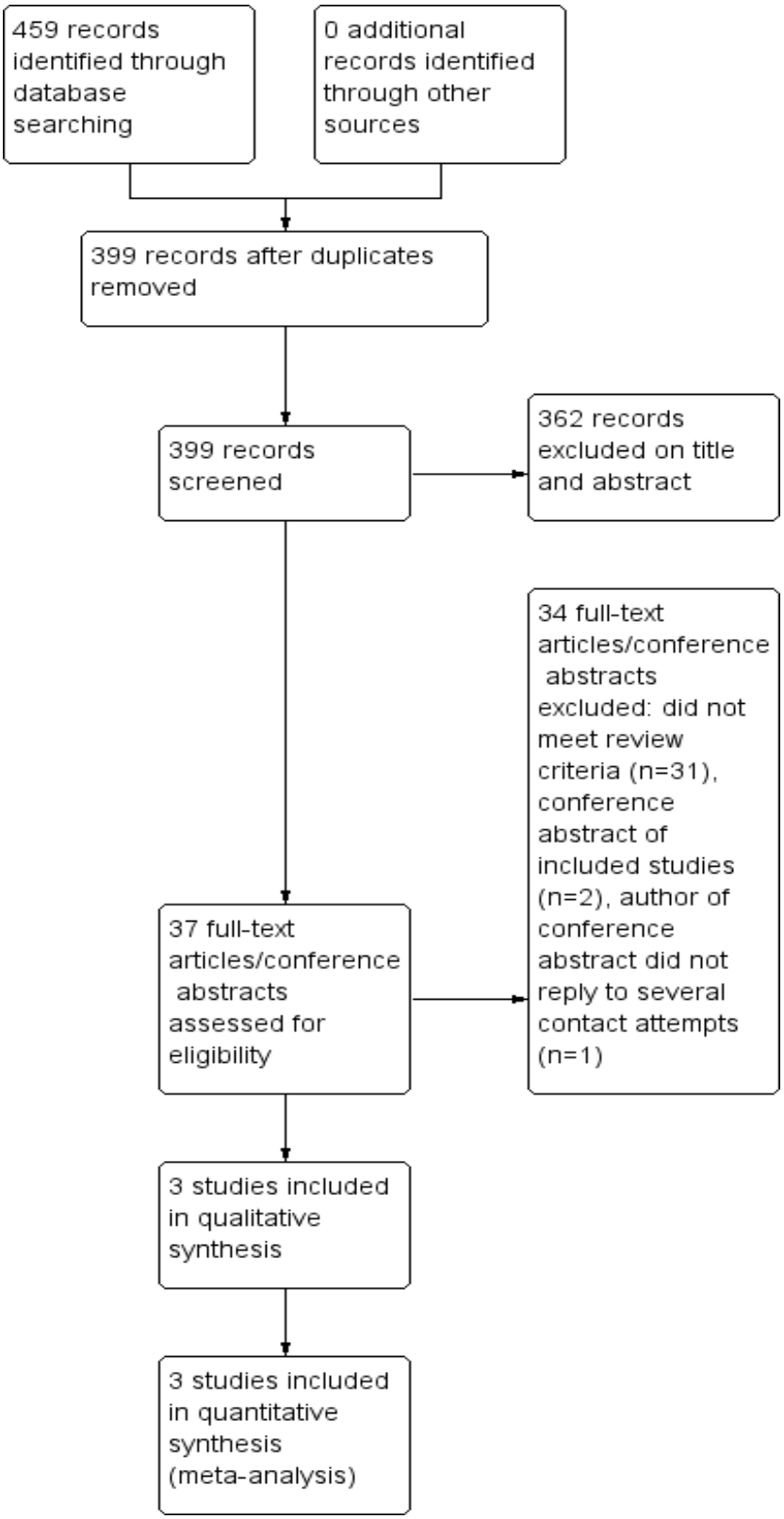

Figure 3-1: Study flow diagram

3.2.3 Included studies

This review comprised three RCTs (36, 101, 260) on 178 participants (Table 2-2). The three studies included only participants with NSCLC following lung resection. The sample size of the included studies ranged from 49 to 78 with the mean age of the participants ranging from 58 to 65 years. Of the 178 participants, 112 (63%) were male and 66 (37%) were female. The studies were based in the UK (36), Denmark (260) and the Netherlands (101). One study is yet to be published (Brocki et al) (260) and the other two were published in 2011 (Arbane et al) (36) and 2013 (Stigt et al) (101).

There was considerable variation in the type, frequency and intensity of the exercise programmes that were investigated. They varied from twice-daily in-patient exercise for 5 days plus 12 weeks of home-based exercises (36) to out-patient programmes (101, 260) that commenced 4 weeks after hospital discharge, conducted twice a week for 12 weeks.

Exercise capacity and HRQoL were the only outcomes that were reported in all three studies. Quadriceps force was reported in one study (36). The studies by Brocki et al (260) and Stigt et al (101) reported lung function as an outcome. Post-operative complications was reported as an outcome in only one study (Arbane et al) (36).

Control groups received usual care that comprised of routine out-patient appointments, pain medication prescription (36, 101), phone calls (36) as well as instructions regarding exercise (260).

3.2.4 Excluded studies

Of the 37 studies for which the full text was reviewed, 34 were excluded for the following reasons: (i) lack of randomisation (18 studies); (ii) investigated the role of exercise training initiated prior to lung resection (six studies); (iii) an intervention other than exercise training (five studies); (iv) conference abstracts of included studies (two abstracts) and (v) mixed population with few participants who underwent lung resection for NSCLC. Two additional studies were excluded as the authors; (i) were unable to provide specific data needed for this review (one study)

and, (ii) did not reply to several contact attempts to obtain the specific data needed for this review (one abstract). These reasons are summarised in Appendix 3 (characteristics of excluded studies).

3.2.5 Risk of bias in included studies

Three out of the seven domains included in the Cochrane Collaboration's 'seven evidence-based domains' table were identical across the four studies (random sequence generation, allocation concealment and blinding of participants and personnel). None studies reported blinding participants or personnel and the domain which had the greatest variation was ‘blinding of outcome assessment’, where one study was rated at low risk of bias (Brocki et al) (260), one at unclear risk of bias (Stigt et al) (101) and the remaining one at high risk of bias (Arbane et al) (36). Intention-to-treat analysis was only reported by Brocki et al (260). For further details see Table 3-2 (risk of bias in included studies) as well as Figure 3-2 (risk of bias graph) and Figure 3-3 (risk of bias summary).

Table 3-2: Risk of bias in included studies

Bias	Arbane 2011	Brocki 2010	Stigt 2013
Random sequence generation (selection bias)	LOW	LOW	LOW
Quote/comment	"…performed using computer generated tables …"	"…We used two computer-generated randomisation tables, stratified for pneumonectomy, since we expected the latter to present with low performance status…"	"…patients were randomised to the active (rehabilitation) group or control group using a computer minimization system…"
Allocation concealment (selection bias)	LOW	LOW	LOW
Quote/comment	"…Randomisation codes were kept by an independent member of the team and released after consent…"	"…Individual allocations were placed by an external person in consecutively numbered and sealed opaque envelopes..."	"…using a computer minimization system initiated by the treating chest physician…" Comment: Investigators enrolling participants could not foresee assignment.
Blinding of participants and personnel (performance bias)	HIGH	HIGH	HIGH
Quote/comment	"…Study was single blinded with the therapist performing assessments	"…No blinding of participants and trainers…"	No blinding of participants and personnel.

	unaware of the randomisation although weekend treatments meant that in about 10 participants the same therapist performed the assessment and treatment…"		
Blinding of outcome assessment (detection bias)	HIGH	LOW	UNCLEAR
Quote/comment	"…Study was single blinded with the therapist performing assessments unaware of the randomisation although weekend treatments meant that in about 10 participants the same therapist performed the assessment and treatment…" Comment: Partial blinding of outcome assessment.	"…Assessors were blinded to the individual group allocation and patients were instructed not to reveal their individual group allocation..."	The study did not address this outcome.
Incomplete outcome data (attrition bias)	LOW	UNCLEAR	HIGH
Quote/comment	Numbers for each outcome were reported. Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.	"Exercise group: Nine participants lost to follow-up (two deceased; two withdrew for not wanting to receive intervention; five withdrew consent for other reasons); 32 completed. Control group: One participant lost to follow-up (deceased); 36 completed.	Three months post discharge six-minute walk distance and lung function data reported for less than 40% and 60% of participants, respectively. Reasons reported as follows: "… because they dropped out or felt unable to perform the test…"

		6MWT n = 34; SF-36 n = 35; spirometry n = 34. Intention-to-treat analysis was done." Comment: Insufficient details about missing cases to permit judgement of 'Low risk' or 'High risk'.	
Selective reporting (reporting bias)	UNCLEAR	UNCLEAR	HIGH
Quote/comment	No protocol available. Insufficient information to permit judgement of 'Low risk' or 'High risk'.	Insufficient information to permit judgement of 'Low risk' or 'High risk'.	The trial registration of the study (http://clinicaltrials.gov/show/NCT01136083) was reviewed and not all of the pre-specified outcomes were reported in the published paper.
Other bias	HIGH	UNCLEAR	HIGH
Quote/comment	Five day post-operative assessment did not include quality of life questionnaire. Also, the control group had five participants categorised at stage IV whereas the exercise group had none.	Insufficient information to permit judgement of 'Low risk' or 'High risk'.	More patients who had chemotherapy were randomised to the training group and table 3 shows a higher drop-out in attendance rate for patients who had chemotherapy compared to patients who did not.

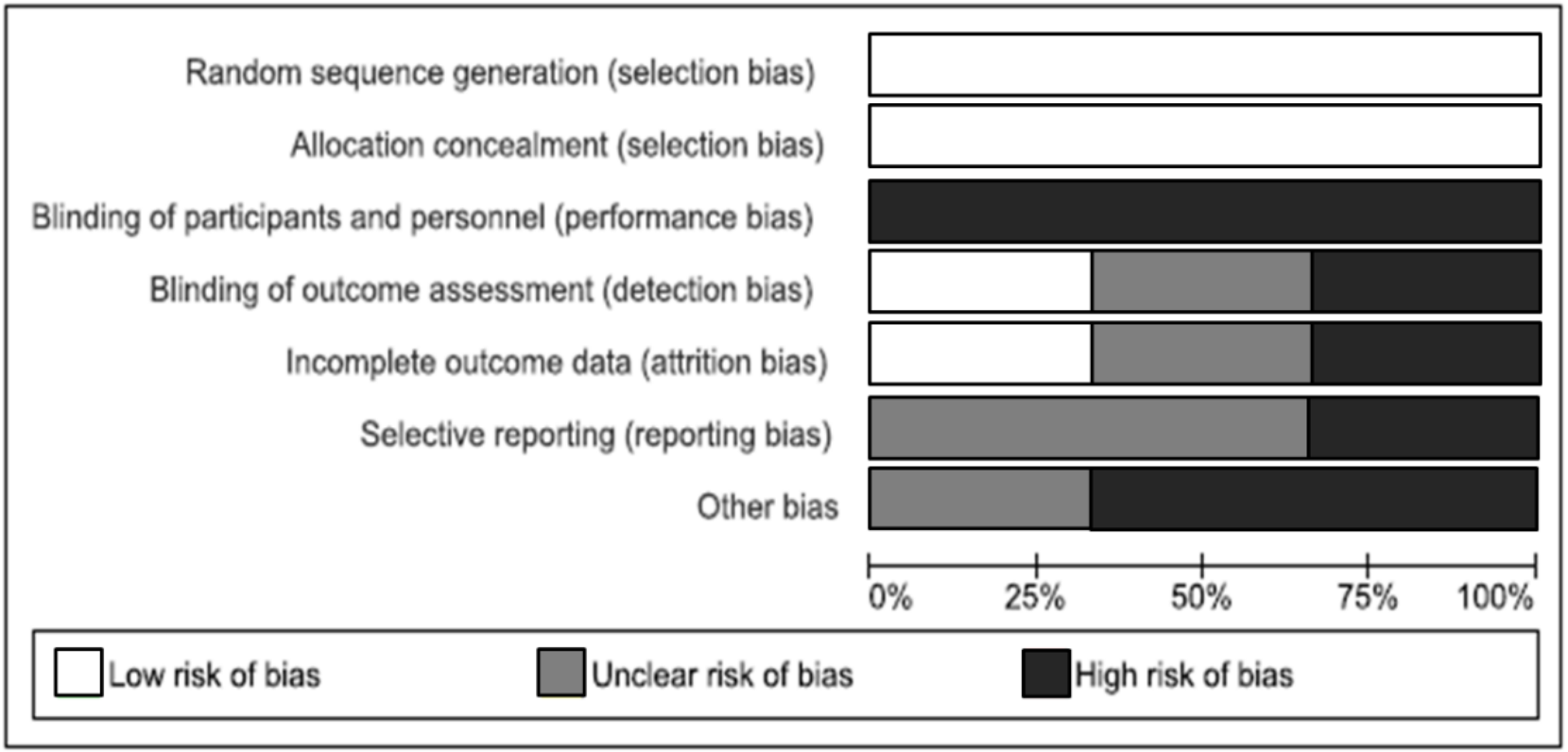

Figure 3-2: Risk of bias graph

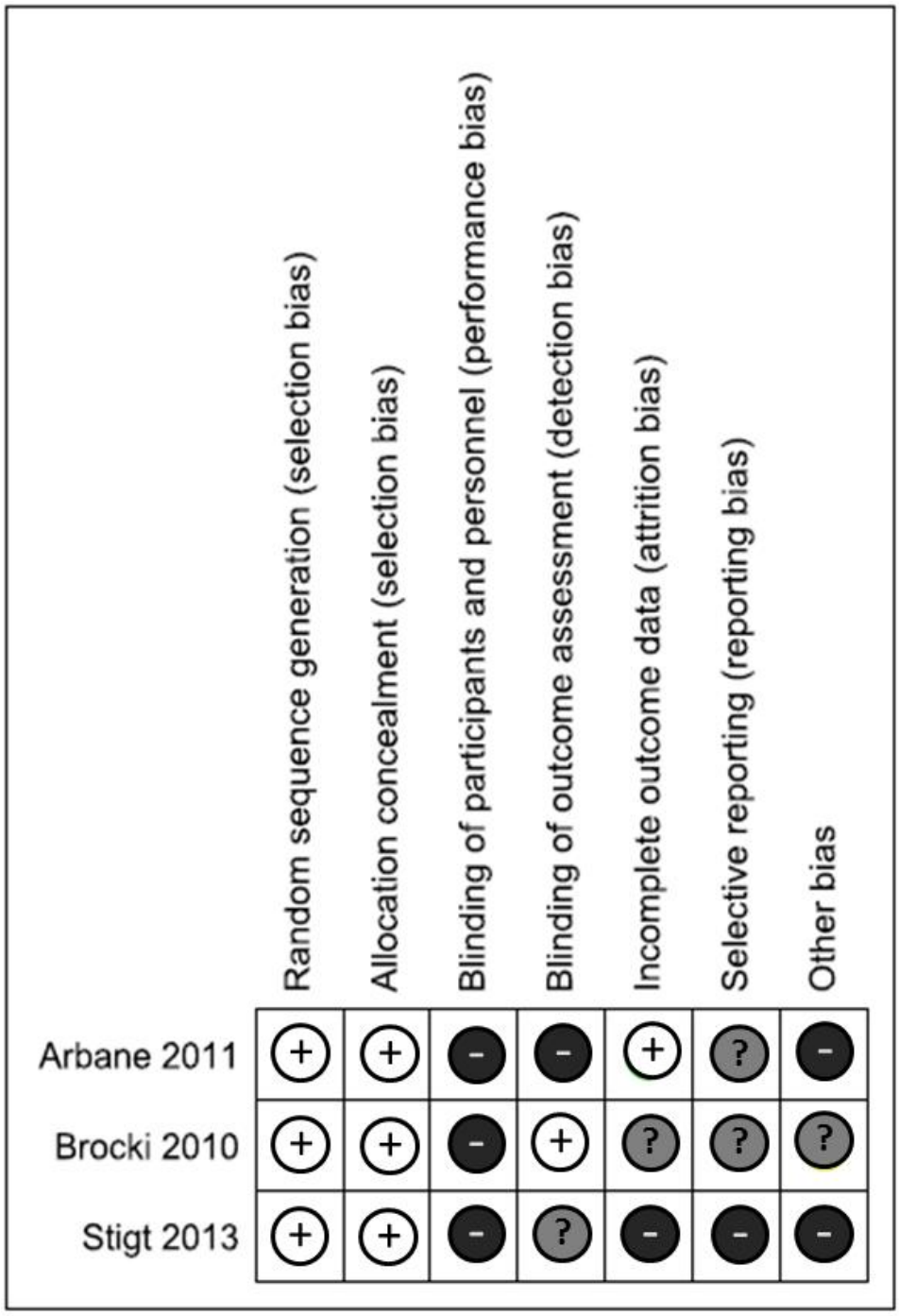

Figure 3-3: Risk of bias summary

3.2.5.1 Allocation (selection bias)

All three studies reported using a process of randomly allocating participants to the two groups. In all studies, this randomisation sequence was concealed. Therefore all the studies were judged to be at low risk of selection bias.

3.2.5.2 Blinding (performance bias and detection bias)

Neither the participants nor the personnel responsible for implementing the intervention were blind to group allocation in any of the included studies. This lack of blinding could have influenced the results as the participants may have been influenced by a placebo effect. Hence, all studies were rated at a high risk of performance bias. Regarding detection bias, in one study (Brocki et al) (260) blinding of the outcome assessor was fully ensured and the study was rated as a low risk of detection bias. As the study by Stigt et al (101) did not describe blinding of outcome assessors, the risk of detection bias was rated as unclear. In the other study (Arbane et al) (36), partial blinding of the outcome assessors was reported. Specifically, in about 10 participants, the same therapist performed the assessments and the intervention and thus this study was judged as high risk of bias.

3.2.5.3 Incomplete outcome data (attrition bias)

One study was rated at low risk of bias due to incomplete outcome data (Arbane et al) (36). This was because missing outcome data was balanced in numbers between the intervention and control groups, with similar reasons for missing data across groups). Although Brocki et al (260) analysed their data according to the intention-to-treat principle, there were no sufficient details about the missing cases to permit judgement of low or high risk of bias. Therefore, this study was rated at unclear risk of bias due to incomplete outcome data. One study was rated at high risk of bias (Stigt et al) (101) mainly due to a large loss to follow-up with some post-intervention data (Table 3-3) reported on only 40% to 60% of participants.

Table 3-3: Studies results

Studies	*Results*
Arbane 2011	***Exercise capacity**: 6MWD:* EG: 21 participants completed; CG: 16 participants completed; Measurements 5 days and 12 weeks (post-intervention) post-operatively: Mean ± SD: EG: 336.7 ± 84.1 m to 480.2 ± 110.0 m; CG: 308.7 ± 124.8 m to 448.2 ± 95.1 m ***Health-related quality of life**: EORTC QLQ-C30:* EG: 22 participants completed; CG: 21 participants completed; Groups were similar preoperatively. No post-operative baseline measures. Measurements 12 weeks post-operative (post-intervention): *EORTC QLQ-C30 (global health):* EG: 68.2 ± 15.3; CG: 68.1 ± 25.1 ***Quadriceps force**: Magnetic stimulation of femoral nerve, in kg:* EG: 17 participants completed; CG: 13 participants completed; Measurements 5 days and 12 weeks (post-intervention) post-operatively. EG: 37.6 ± 27.1 kg to 34.2 ± 9.4 kg; CG: 21.5 ± 7.7 kg to 26.4 ± 9.7 kg;
Brocki 2010 ***(unpublished)**	***Exercise capacity**: 6MWD:* EG: 32 participants completed; CG: 34 participants completed; Post-operative measurements: baseline and post-intervention: Mean ± SD: EG: 426.8 ± 123.6 m to 506.9 ± 128.4 m; CG: 407.2 ± 101.5 m to 464.5 ± 97 m ***Health-related quality of life**: SF-36 questionnaire:* EG: 32 participants completed; CG: 35 participants completed; Post-operative measurements: baseline and post-intervention: *SF-36 (physical component):* EG: 45.7 ± 10 to 50.8 ± 8.8; CG: 44.9 ± 8.9 to 50.2 ± 9.1 ***Lung function**: FEV_1:* EG: 32 participants completed; CG: 34 participants completed; Post-operative measurements: baseline and post-intervention: EG: 1.75 ± 0.5 L to 1.87 ± 0.5 L; CG: 1.9 ± 0.6 L to 2.06 ± 0.6 L

Stigt 2013	***Exercise capacity**: 6MWD:* EG: 8 participants; CG: 11 participants; No post-operative baseline measures. Measurements 3 months post-operative (post-intervention): Mean ± SD: EG: 567 ± 78 m; CG: 491 ± 109 m ****Health-related quality of life**: SGRQ:* EG: 22 participants; CG: 22 participants; Post-operative measurements: baseline and post-intervention: EG: 34.6 ± 18.4 to 29.8 ± 15.7; CG: 30.7 ± 20.7 to 26.9 ± 19.1 ****Lung function**: FEV_1 :* EG: 9 participants completed; CG: 14 participants completed; Groups were similar preoperatively. No post-operative baseline measures. Measurements 3 months post-operative (post-intervention): EG: 2.1 ± 0.6 L; CG: 2 ± 0.6 L

Abbreviations: 6MWD: six-minute walk distance; CG – Control group; EG – Exercise group; EORTC QLQ-C30 - European organisation for research and treatment of cancer quality of life questionnaire core 30; FEV_1 – Forced expiratory volume in one second; SF-36 - Medical outcomes study short form 36 general health survey ; SGRQ - St. George's respiratory questionnaire.
*Data provided by the author

3.2.5.4 Selective reporting (reporting bias)

Two studies (Arbane et al and Brocki et al) (36, 260) were judged to be at unclear risk of bias due to selective reporting because there was insufficient information to judge this item (i.e. no access to trial's registry). The trial registration of the study by Stigt et al (101) (http://clinicaltrials.gov/show/NCT01136083) was reviewed and not all of the pre-specified outcomes were reported. Therefore, the study was rated at high risk of bias due to selective reporting.

3.2.5.5 Other potential sources of bias

The two published studies were rated at high risk of bias due to other sources of bias. The potential sources of bias were as follows: (i) two studies (Arbane et al and Stigt et al) (36, 101) did not collect all outcome measures at identical time points; (ii) the control group of the first study (36) had five participants classified as stage IV NSCLC whereas the intervention group had none in this stage and (iii) Stigt et al (101) had more participants following chemotherapy randomised to the intervention group and there was a higher attrition rate for those who had chemotherapy compared to those who did not.

3.2.6 Effects of interventions

The mean and standard deviation for difference in outcome measures collected at baseline (i.e. following lung resection but prior to the commencement of the intervention) and post-intervention were not available in any of the studies. Therefore, the meta-analysis was performed using post-intervention data for those studies in which no significant differences between control group and intervention group were reported either; (i) prior to lung resection or, (ii) following lung resection, but prior to the commencement of the intervention period. Exercise capacity, HRQoL and lung function (FEV_1) data were included in both the meta-analysis and in the 'Summary of findings' table (Table 3-4). A narrative summary for quadriceps force and development of post-operative complications is presented.

Table 3-4: Summary of findings table

Exercise training for people following lung resection for non-small cell lung cancer				
Patient or population: People following lung resection for non-small cell lung cancer **Settings:** In-patient or out-patient hospital departments **Intervention:** Exercise training				
Outcomes	**Illustrative comparative risks* (95% CI)**		**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**		
	Control	**Exercise training**		
Exercise capacity 6MWD Follow-up: 2 to 3 months	The mean exercise capacity ranged across control groups from **448 to 491 m**	The mean exercise capacity in the intervention groups was **50.35 higher** (15.45 to 85.24 higher)	139 (3 studies)	⨁⨁⨁⊖ **low**[1,2]
Health-related quality of life Follow-up: 2 to 3 months	The mean health-related quality of life ranged across control groups from **42.2 to 73.1**	The mean health-related quality of life in the intervention groups was **0.17 higher** (0.16 lower to 0.49 higher)	147 (3 studies)	⨁⨁⨁⊖ **low**[1,2]
Lung function Spirometry (FEV_1 in litres) Follow-up: 2 to 3 months	The mean lung function ranged across control groups from **2.00 to 2.06 L**	The mean lung function in the intervention groups was **0.13 lower** (0.36 lower to 0.11 higher)	89 (2 studies)	⨁⨁⨁⊖ **low**[1,2]
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval;				
GRADE Working Group grades of evidence **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate. [1] Some significant risk of bias across the studies; [2] Small sample sizes across the studies				

3.2.6.1 Primary outcome: Exercise capacity

All three studies reported the 6MWD as their measure of exercise capacity (Table 3-1). On completion of the intervention period, exercise capacity was significantly higher in the intervention group compared to the control group (MD [95% CI] 50 [15 to 85] m; Figure 3-4).

3.2.6.2 Secondary outcome: Health-related quality of life

All three studies reported measures of HRQoL (Table 3-1); one used the EORTC QLQ-C30 (Arbane et al) (36), one used the SGRQ (Stigt et al) (101) and one used the SF-36 (Brocki et al) (260). On completion of the intervention period, there was no significant difference in HRQoL between intervention and control groups (SMD [95% CI] 0.17 [-0.16 to 0.49]; Figure 3-5).

3.2.6.3 Secondary outcome: Lung function (FEV_1)

Two studies reported measures of lung function (Brocki et al and Stigt et al) (101, 260) (Table 3-1). On completion of the intervention period, there was no significant difference in FEV_1 between intervention and control groups (MD [95% CI] -0.13 [-0.36 to 0.11] L; Figure 3-6).

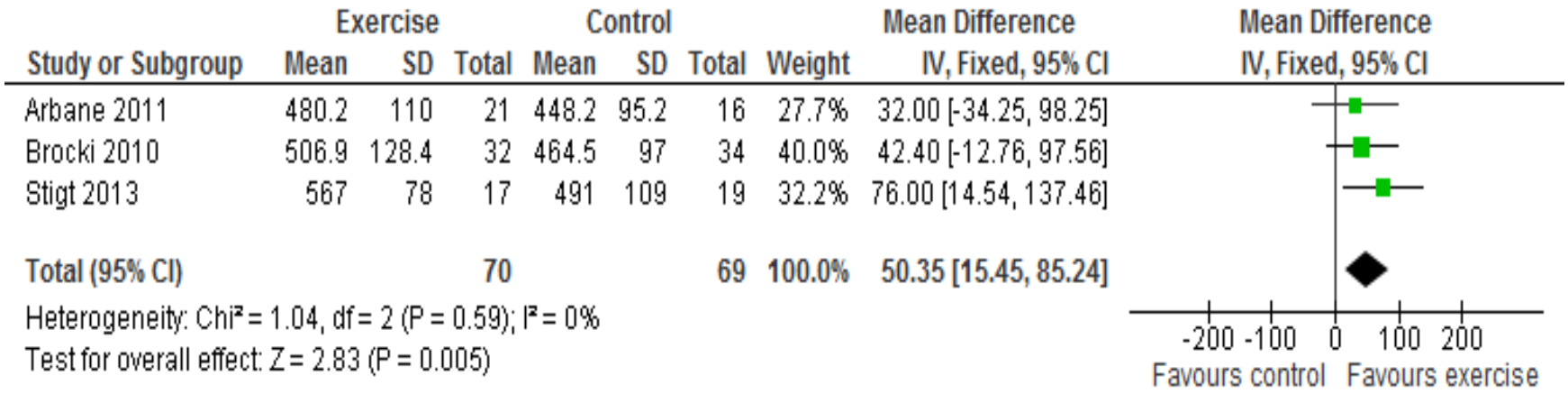

Figure 3-4: Forest plot of comparison: Exercise group vs control group. Outcome: Exercise capacity (six-minute walk distance).

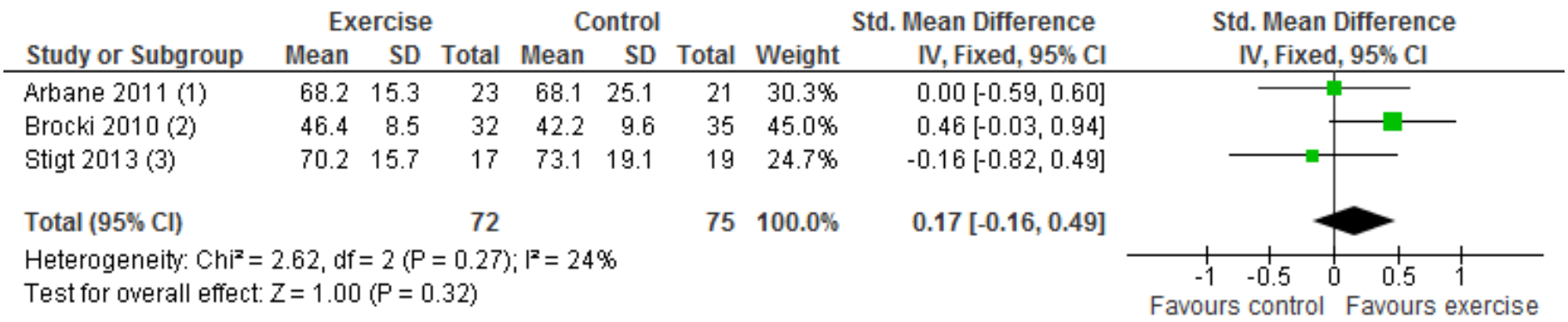

Figure 3-5: Forest plot of comparison: Exercise group vs control group. Outcome: Health-related quality of life.

Abbreviations: EORTC QLQ-C30 - European organisation for research and treatment of cancer quality of life questionnaire core 30; SF-36 - Medical outcomes study short form 36 general health survey ; SGRQ - St. George's respiratory questionnaire.

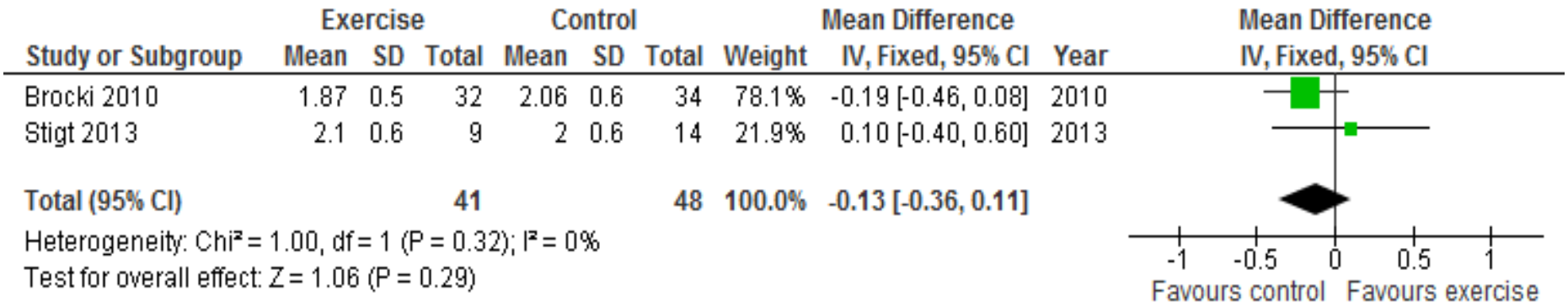

Figure 3-6: Forest plot of comparison: Exercise group vs control group. Outcome: Lung function (forced expiratory volume in one second).

3.2.6.4 Secondary outcome: Quadriceps force

Only one study (Arbane et al) (36) measured quadriceps force (Table 3-1). The researchers measured quadriceps force as twitch force elicited via magnetic stimulation of the femoral nerve. This study demonstrated no differences between groups on completion of the 12 week intervention.

3.2.6.5 Development of a post-operative pulmonary complication

Only one study commenced the intervention period during the in-patient stay immediately following lung resection (Arbane et al) (36). This was the only study to report post-operative complications. There were two complications following lung resection in the intervention group and three in the control group; the nature of these complications was not specified in the paper.

3.2.6.6 Secondary outcomes: Pressure-generating capacity of respiratory muscles, dyspnoea, fatigue, feelings of anxiety and depression and mortality

Data were not available for these outcomes.

3.3 Discussion

This review aimed to determine the effects of exercise training on exercise capacity, HRQoL, FEV_1 and quadriceps force, in people following lung resection for NSCLC. Data from three RCTs and 178 participants were included. The meta-analyses demonstrate that exercise training conferred an increase in exercise capacity, measured as 6MWD (MD [95% CI] 50 [15 to 85] m), in this population. However, there was no statistical difference in HRQoL or lung function. There was insufficient data to comment on the effect of exercise training on quadriceps force. The findings of this systematic review should be interpreted with caution due to disparities between the studies, methodological limitations, some significant risks of bias and small sample sizes.

The exercise capacity of people with NSCLC is adversely affected by several factors including the tumour itself, co-existing lung disease as well as treatment for the condition, which may include resection of the tumour with or without adjuvant

chemo/radiotherapy (261). Deconditioning is triggered by disruption in pulmonary mechanics and gas exchange (10), weight loss, protein catabolism and muscle wasting. Consequently people with any type of cancer tend to live very inactive lifestyles (262). Several single-group interventional studies, published in the past 7 years, have shown that exercise training is safe and feasible and may confer benefit for people following resection for lung cancer (28-31, 249). These studies have recommended that large RCTs are undertaken to provide more conclusive evidence regarding the role of exercise training in this population.

In this review, two recently published RCTs as well as data from one unpublished study were included. Even though there was disparity in both the timing and nature of the exercise training as well as the time-points at which outcome measures were assessed, pooled analysis demonstrated a statistically significant effect of exercise training on exercise capacity, measured as the 6MWD (MD [95% CI] 50 [15 to 85] m). In people with NSCLC, the minimal clinically important difference (MCID) for the 6MWD has not been published. Nevertheless, a MD of 50 m exceeds the MCID for 6MWD in people with chronic obstructive pulmonary disease (COPD) (30 m (83) and 35 m (263)) and parenchymal lung disease (29 to 34 m) (78) and, therefore, may be considered important in those following lung resection for NSCLC. An increase in 6MWD following exercise training is an important finding because this measure appears to be a valuable prognostic indicator for people with NSCLC (264).

The current review suggests that exercise training has little effect on HRQoL for people following lung resection for NSCLC. This contrasts with earlier work in people with COPD (19, 23) and interstitial lung disease (20) in which improvements in HRQoL have been demonstrated following exercise training. Nonetheless, the lack of improvement in HRQoL seen in this review is consistent with studies in people with other types of cancer. That is, Markes et al (265) demonstrated limited evidence for the effectiveness of exercise training to change HRQoL for women undergoing treatment for breast cancer. Although it is possible that exercise training is not effective at improving HRQoL in breast or lung cancer, these findings might also relate to limitations in the way HRQoL was assessed. In the current review, two included studies did not use disease-specific HRQoL questionnaires, which are likely to be more responsive to changes in this outcome compared with generic HRQoL

questionnaires. The lack of improvement in HRQoL may also reflect that the meta-analysis lacked statistical power to detect small changes HRQoL. Larger RCTs using disease-specific HRQoL questionnaires are needed to further investigate the effects of exercise training on HRQoL in people following lung resection for NSCLC.

Changes in lung function (FEV_1) following exercise training were not demonstrated in this review. This is in agreement with the literature pertaining to effect of exercise training on lung function in people with COPD (19).

3.3.1 Summary of main results

This review showed that, for people who required lung resection for NSCLC, exercise training conferred a statistically significant improvement in exercise capacity (MD [95% CI] 50 [15 to 85] m). However, this review did not find any evidence that exercise training improved other outcomes such as HRQoL, lung function and quadriceps force.

3.3.2 Overall completeness and applicability of evidence

A recent survey that described pre- and post-operative physiotherapy management for people with lung cancer across Australia and New Zealand (248) reported that only a small proportion of people were referred to exercise training programmes following lung resection. The current review suggests that healthcare professionals should consider referring people following lung resection for NSCLC to an exercise training programme particularly for those with marked decrements in exercise capacity. Exercise training has the potential to interrupt the ‘deconditioning storm’ (15) induced by the disease and its treatment.

3.3.3 Quality of the evidence

The quality of the evidence of the studies included in the analysis has been rated as poor, mainly due to some significant risks of bias and small sample sizes. Specifically, blinding of outcome assessors was only ensured by one of the studies (Brocki et al) (260). Pertaining to performance bias, all the studies were rated as high risk of bias. However, blinding study participants to treatment allocation in RCTs of exercise training is very difficult, as even with ‘sham’ training participants are often

aware of whether or not they are exercising. Likewise, study personnel implementing the intervention are aware of whether or not the participants are exercising. The low number of studies also negatively impacted the quality of the evidence. The inclusion of data from future RCTs will improve the statistical power and precision of the estimates for impact of exercise in this population.

3.3.4 Potential biases in the review process

Strengths of this review relate to the extensive electronic search, search strategy with no language limitation and use of two review authors to independently examine and select studies, as well as the success with contacting the authors of the four included studies to provide additional data. Although attempts to contact authors from two other studies were made, one did not reply and the other did not have access to the data requested. Exclusion of these studies is a potential source of bias.

3.3.5 Agreements and disagreements with other studies or reviews

Only one published systematic review on the effects of exercise training for people with NSCLC was found (266). This previous review included randomised and non-randomised controlled trials and considered studies that provided an exercise intervention to people with NSCLC prior to lung resection as well as following lung resection. Only one RCT of exercise training following lung resection for NSCLC was included in this earlier review (36). Based mainly on the results of 11 non-randomised controlled trials, Granger et al (266) concluded that for people with NSCLC, exercise training implemented either before and after cancer treatment was safe and that exercise training may confer positive benefits on exercise capacity and some domains of HRQoL. The current systematic review is the first to show the effects of exercise training following lung resection for NSCLC using higher level evidence.

3.4 Conclusions

3.4.1 Implications for practice

Evidence from this meta-analysis suggests that exercise training, that included aerobic and resistance exercises, may potentially increase exercise capacity of people

following lung resection for NSCLC. Although the quality of the evidence is low, referrals to exercise training programmes should be considered for this population. This is especially true for those with impairments in exercise capacity. Larger RCTs with good methodological quality, intention-to-treat analysis and proper imputation are needed to confirm the efficacy of exercise intervention in people with NSCLC.

3.4.2 Implications for research

This systematic review emphasises the need for larger RCTs and ongoing investigation of the effects of exercise training following lung resection for NSCLC. As blinding study participants and personnel in RCTs of exercise training is very difficult, even with 'sham' training, efforts have to be done to, at least, ensure blinding of outcome assessors. Intention-to-treat analysis as well as attempts to minimise loss to follow-up should also be considered by upcoming studies.

In order to minimise methodological heterogeneity and advance knowledge in this field, future RCTs should consider: (i) collecting outcome measures immediately before and after the exercise training intervention, rather than before lung resection and on completion of the exercise training intervention; (ii) choosing disease-specific HRQoL questionnaires; (iii) reporting the values for each domain that contributes to HRQoL as well as the total score obtained from HRQoL questionnaires and; (iv) reporting data pertaining to the mean change (and standard deviation of the change) in outcomes collected immediately before and after the exercise training intervention. Exploring other variables such as fatigue, dyspnoea, and anxiety and depression, are also likely to be of value.

CHAPTER 4

PHYSIOTHERAPY PRACTICE PATTERNS FOR PATIENTS UNDERGOING SURGERY FOR LUNG CANCER: A SURVEY OF HOSPITALS IN AUSTRALIA AND NEW ZEALAND

Overview

This Chapter presents the methodology of the survey performed as part of this programme of research. A description of the sample surveyed as well as of the questionnaire developed is given. Details of the methods of approach employed as well as data management and analyses used are described. The study presented in this Chapter has been already published in Internal Medicine Journal (248).

The specific question answered in this Chapter is: What are the current physiotherapy practice patterns for people undergoing lung resection for lung cancer in Australia and New Zealand?

4.1 Methods

4.1.1 Sample

Hospitals in Australia and New Zealand that provide thoracic surgery and physiotherapy services were identified using internet searches. That is, a list of major hospitals in Australia (http://en.wikipedia.org/wiki/List_of_hospitals_in_Australia) and New Zealand (http://en.wikipedia.org/wiki/List_of_hospitals_in_New_Zealand) was identified and, thereafter, individual hospital websites were examined to determine whether or not they provide thoracic surgery services. The list produced by this search was cross-referenced against one provided by the authors of a previous

study (37). Inconsistencies in the eligible sites between the two lists were resolved by contacting the hospitals directly.

4.1.2 Survey Instrument

A questionnaire was developed (Appendix 4) to collect information pertaining to characteristics of the hospitals and staff, the types of assessments completed prior to surgery as well as physiotherapy management both before and after resection of lung cancer. The questionnaire was piloted by four experienced physiotherapists in order to optimise its face validity, readability and structure. Thereafter, the questionnaire was sent to two physiotherapists with a doctoral degree in the area of cardiorespiratory practice who were asked to comment on the layout, terminology and content. The final version of the questionnaire comprised three sections, consisted of 22 questions, and took approximately 15 minutes to complete.

4.1.3 Approach

The Tailored Design Method (Dillman approach) (267) was used as it has been previously shown to reduce survey error and optimise response rate. The first contact with each hospital was with the manager of the physiotherapy department via email. If no response was obtained within 4 weeks, a reminder email was sent and this person was contacted via the telephone. The manager was asked to nominate the physiotherapist who had the most contact with patients who require thoracic surgery for lung cancer in their department (i.e. a senior cardiothoracic physiotherapist). Once identified, this physiotherapist was sent a letter (both via post and email) outlining the purpose and aims of the study. The questionnaire was then posted with a reply-paid envelope. For those who agreed to participate, 4 weeks were allowed for return of the questionnaire after which time a reminder letter was sent via email. Physiotherapists were asked not to answer questions if they were unsure of the correct response and were encouraged to contact other members of the healthcare team to seek information as appropriate. Where responses were not completed, the physiotherapist was contacted by telephone in an attempt to ascertain the most appropriate answer to each question.

Approval was granted from the Human Research Ethics Committee at Curtin University (approval number PT0185). Return of the questionnaire was taken as informed consent.

4.1.4 Statistical analyses

Responses were numerically coded for descriptive summaries and reporting of frequency. Analyses were undertaken using the Statistical Package for the Social Sciences (SPSS), version 19.0.

4.2 Results

A total of 54 hospitals (46 in Australia and eight in New Zealand) were deemed eligible to participate in the study. Staff in the physiotherapy department at five hospitals did not respond to our repeated attempts to make contact (i.e. emails, faxing and phone calls). Hence, 49 questionnaires were mailed out (43 to hospitals in Australia and 6 to hospitals in New Zealand). Staff from two sites declined participation after receiving the questionnaire as surgical resection for lung cancer was no longer performed at their facility. Of the 47 sites where both initial contact was made and surgical services for patients with lung cancer were provided, a total of 43 questionnaires were returned, yielding a response rate of 91%. The four questionnaires that were not returned were all from private hospitals. Data pertaining to the distribution of hospitals are provided in Table 4-1.

4.2.1 Characteristics of the physiotherapists and hospitals

Most respondents (n = 35; 81%) had more than 5 years of clinical experience with 31 (72%) having more than 5 years of experience treating patients with respiratory diseases. Thirty-three (77%) respondents had completed their entry level qualification in Australia, with a smaller proportion from the United Kingdom (n = 5; 12%), New Zealand (n = 4; 9%) and the Republic of Ireland (n = 2; 5%). The majority of respondents held a bachelor's degree as their highest tertiary qualification (n = 35; 84%). The number of patients with lung cancer who underwent surgery in the past month is shown in Table 4-2.

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Table 4-1: Numbers and distribution of hospitals on a state-by-state basis

	Deemed eligible (n=54)	Public / Private (n=35 / 19)	Responded to contact attempts (n=49)	*Declined participation (n=2)	Included in the analysis (n=47)	Questionnaires returned (n=43)
Australia	**46**	**30 / 16**	**43**	**2**	**41**	**37**
ACT	2	2 / 0	2	0	2	2
NSW	17	9 / 8	16	1	15	13
QLD	4	3 / 1	4	0	4	4
SA	5	3 / 2	5	0	5	5
NT	0	-	-	-	-	-
TAS	1	1 / 0	1	0	1	1
VIC	13	9 / 4	11	1	10	8
WA	4	3 / 1	4	0	4	4
New Zealand	**8**	**5 / 3**	**6**	**0**	**6**	**6**
NI	6	3 / 3	4	0	4	4
SI	2	2 / 0	2	0	2	2

Abbreviations: ACT – Australian Capital Territory; NSW – New South Wales; QLD – Queensland; SA – South Australia; NT – Northern Territory; TAS – Tasmania; VIC – Victoria; WA – Western Australia; NI – North Island; SI – South Island.
* Declined participation after receiving the questionnaire.

Table 4-2: Number of patients with lung cancer who underwent surgery in the past month (n = 43)

Number of patients	*Lobectomy*	*Pneumonectomy*
< 4	15 (35%)	41 (95%)
4 - 8	16 (37%)	1 (2.5%)
9 - 12	5 (12%)	0 (0%)
> 12	5 (12%)	0 (0%)
Unsure	2 (5%)	1 (2.5%)

4.2.2 Pre-operative assessment, education and exercise training

The majority of respondents stated that the most common assessments completed by patients prior to surgery were spirometry (n = 36; 84%) and computerised tomography (CT) scans (n = 31; 72%). Patients in 16 hospitals (37%) usually underwent measures of single breath diffusing capacity for carbon monoxide (D_LCO) and five respondents (12%) stated that the CPET was routinely measured at their facility. Measures of health-related quality of life (HRQoL) and six-minute walk distance (6MWD) were collected at two sites (5%) with the exercise responses via a stair climbing test and maximal respiratory pressures assessed at one hospital each. Eight respondents reported collecting "other" measures such as blood tests, urine tests, the positron emission tomography scan, bronchoscopy/mediastinoscopy and CT-guided biopsy.

The involvement of the physiotherapists in the pre-operative assessment and education of patients with lung cancer undergoing surgery is shown in Figure 4-1. In 40% (n = 17) of the hospitals, respondents indicated that patients were not assessed by a physiotherapist prior to resection for lung cancer. Nine respondents (21%) reported assessing all patients with lung cancer before surgery. When assessments were undertaken, common procedures comprised auscultation, cough, subjective reports of exercise tolerance, and spirometry. Pre-operative education was provided by physiotherapists to all of the patients in 19 hospitals (44%); the topics are summarised in Table 4-3.

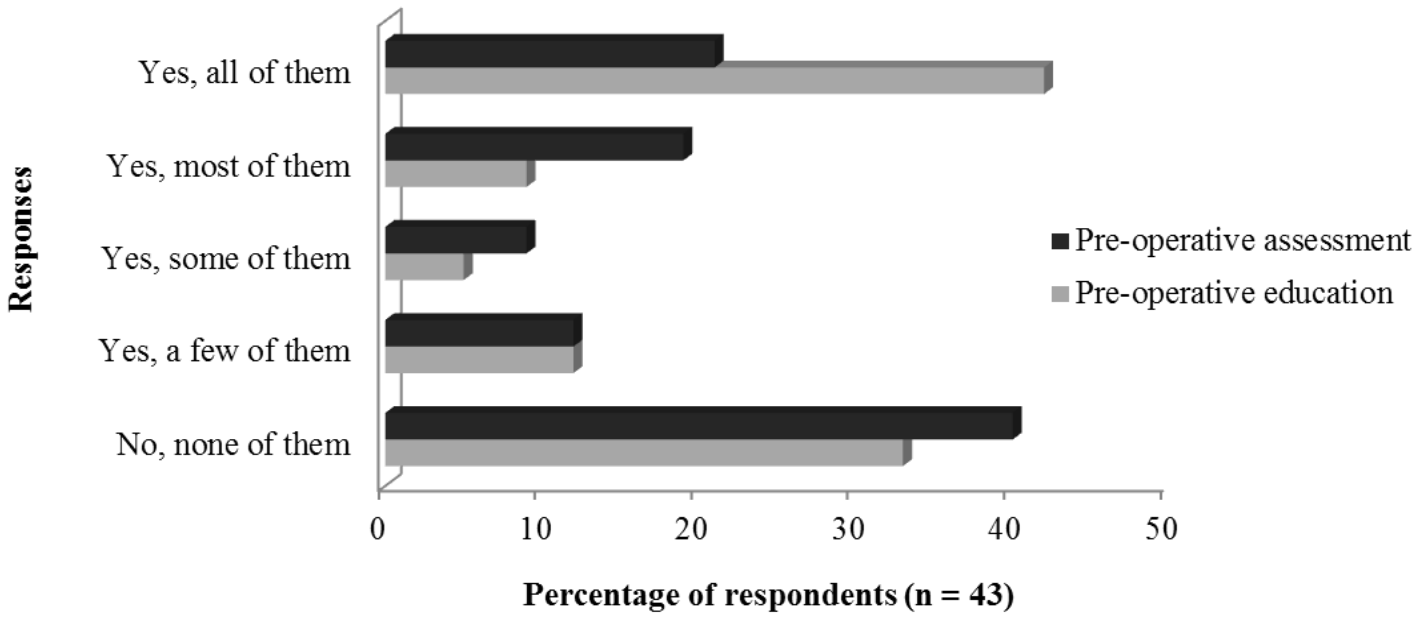

Figure 4-1: Percentage responses to questions: (i) are you involved in the pre-operative assessment of patients with lung cancer undergoing surgery? (response in black bars) and, (ii) are you involved in the pre-operative education of patients with lung cancer undergoing surgery? (response in grey bars).

Table 4-3: Topics covered as part of pre-operative education.

	Proportion of patients who were provided with pre-operative education				
Topic; *n (%)*	None of them	A few of them	Some of them	Most of them	All of them
Breathing techniques (n=30)	1 (3%)	4 (13%)	4 (13%)	3 (10%)	18 (60%)
Cough/huff (n=30)	0 (0%)	5 (17%)	3 (10%)	4 (13%)	18 (60%)
Explanation about the importance of upright positioning (n=30)	1 (3%)	6 (20%)	2 (7%)	3 (10%)	18 (60%)
Explanation about the importance of early ambulation (n=30)	0 (0%)	4 (13%)	3 (10%)	4 (13%)	19 (63%)
Shoulder exercises (n=29)	1 (3%)	7 (24%)	4 (14%)	2 (7%)	15 (52%)
Thoracic range of movement exercises (n=29)	4 (14%)	7 (25%)	5 (18%)	3 (11%)	9 (32%)
Explanation of post-operative physiotherapy sessions (n=29)	0 (0%)	4 (13%)	3 (10%)	3 (10%)	20 (67%)
***Other:**	1 (3%)	0 (0%)	2 (7%)	0 (0%)	8 (28%)

n (physiotherapists who answered that do not provide education were excluded from the analysis);
*Other : lifting + wound precautions / mobility and exercise tolerance assessment / side lying (contralateral side) - pain relief / circulation exercises.

Four respondents (9%) reported that pre-operative exercise training was provided in their hospitals to a 'few' patients. In these hospitals, it was most often the surgeon who initiated the referral.

4.2.3 Post-operative management

The majority of respondents (n = 39; 91%) reported that patients commenced physiotherapy on the first post-operative day with four (9%) responding that patients were routinely treated on the day of surgery. Table 4-4 summarises the types of exercises/techniques implemented by physiotherapists as part of post-operative patient care. The most common treatments applied to all patients were walking exercises, cough/huff and breathing techniques. Following surgery, 40 respondents (93%) reported that all patients participated in walking exercise and in most facilities (n = 38; 88%) this was initiated as part of an early mobilisation programme by the physiotherapist. Cough/huff and breathing techniques were also used frequently as post-operative techniques for all patients (n = 36; 84% and n = 35; 81%, respectively). Of the 13 respondents (30%) that included 'other' exercises in the answer, 10 described shoulder range of motion and thoracic exercises as techniques undertaken by the physiotherapists.

Figure 4-2 shows the proportion of patients referred to outpatient exercise training programmes (pulmonary rehabilitation). Seventy-two per cent of respondents (n = 31) refer less than 25% of patients to exercise training on discharge from hospital. Of these, two respondents mentioned that the existing pulmonary rehabilitation programmes in their region do not accept patients with a diagnosis other than chronic obstructive pulmonary disease. Respondents were asked to indicate (on a five-point Likert scale) which factors had most influenced their management of patients with lung cancer. The results are shown in Table 4-5.

Table 4-4: Types of exercises/techniques used following surgery.

	Proportion of patients receiving the described exercises/techniques				
Exercises/techniques; *n (%)*	None of them	Few of them	Some of them	Most of them	All of them
Breathing techniques	1 (2%)	1 (2%)	5 (12%)	1 (2%)	35 (82%)
Airway clearance techniques (other than cough/huff)	4 (9%)	8 (19%)	15 (35%)	3 (7%)	13 (31%)
Cough/huff	1 (2%)	1 (2%)	1 (2%)	4 (9%)	36 (84%)
Inspiratory muscle training	30 (70%)	6 (14%)	2 (5%)	2 (5%)	3 (7%)
Aerobic (walking)	0 (0%)	0 (0%)	0 (0%)	3 (7%)	40 (93%)
Aerobic (cycling)	29 (67%)	9 (21%)	5 (12%)	0 (0%)	0 (0%)
Strength (lower limbs)	15 (35%)	12 (28%)	8 (19%)	4 (9%)	4 (9%)
Strength (upper limbs)	20 (46%)	7 (16%)	10 (23%)	2 (5%)	4 (9%)
***Other:**	0 (0%)	0 (0%)	1 (2%)	4 (10%)	8 (19%)

* Other – the other topics mentioned were: shoulder range of movement and thoracic exercises (24%); posture re-education (2%); CPAP – NIV (2%) and stair climbing (2%).

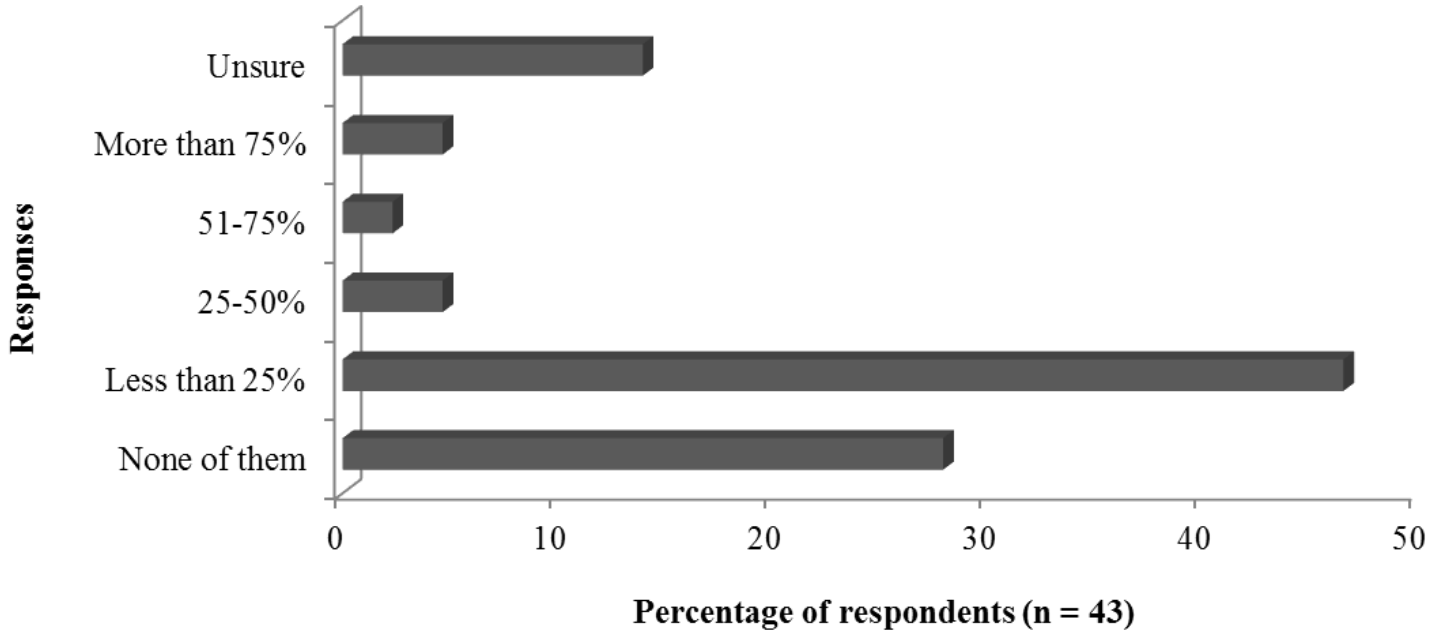

Figure 4-2: Proportion of patients referred to outpatient exercise training programmes (pulmonary rehabilitation).

Table 4-5: Factors influencing physiotherapy management of patients with lung cancer.

Influencing Factor; *n (%)*	Not at all	A little	Somewhat	A lot	Very much
Published journal articles (n=41)	0 (0%)	8 (19%)	18 (44%)	13 (32%)	2 (5%)
Text books (n=41)	3 (7%)	14 (34%)	15 (37%)	5 (12%)	4 (10%)
Established practice in your hospital (n=43)	0 (0%)	4 (9%)	12 (28%)	15 (35%)	12 (28%)
Personal experience (n=42)	0 (0%)	1 (2%)	9 (21%)	18 (43%)	14 (33%)
Postgraduate education (n=38)	12 (32%)	7 (18%)	14 (37%)	4 (10%)	1 (3%)
Professional development (workshops, seminars etc.) (n=42)	4 (10%)	6 (14%)	21 (50%)	8 (19%)	3 (7%)
Initial academic education (n=41)	3 (7%)	13 (32%)	14 (34%)	7 (17%)	4 (10%)
***Other please specify:**	0 (0%)	1 (2%)	0 (0%)	0 (0%)	2 (5%)

* Other: protocol specified by the surgeon (twice) and intensive care consultant (once).

4.3 Discussion

This survey detailed the current management and practice patterns of Australia's and New Zealand's physiotherapy services for people undergoing resection for lung cancer. The main findings were that (i) prior to surgery, in 40% of the hospitals, patients were not assessed by a physiotherapist; (ii) the majority of respondents did not provide pre-operative exercise training for patients with lung cancer; (iii) post-operatively, physiotherapy was most commonly commenced on the day following surgery with walking-based exercise being the most frequently implemented treatment and; (iv) on discharge from hospital, 72% of respondents referred less than 25% of patients to exercise training programmes. Our response rate of 91% is greater than that achieved by previous studies, conducted in the same countries, in the area of physiotherapy for patients following thoracic surgery (response rate = 80%) (37), pulmonary rehabilitation (response rate = 83%) (268) and cancer care (response rate = 51%) (269). The high response rate suggests that our results are unlikely to be influenced by a responder bias and thereby provide a representative snapshot of current physiotherapy practice patterns for patients with lung cancer across in Australia and New Zealand.

4.3.1 Pre-operative assessment, education and exercise training

International guidelines (73, 169, 270, 271) recommend that the risk of peri- and post-operative complications for those individuals who have a resectable tumour be based, at least in part, on measures of lung function and exercise capacity. The finding of the current survey that showed that forced expiratory volume in one second (FEV_1) and D_LCO were the most commonly used pre-operative assessments in this population is in agreement with these guidelines. The CPET is recommended to further refine the peri-operative risk of surgery for patients with predicted post-operative values for either FEV_1 or D_LCO of below 40% (73, 169). Of note, a peak rate of oxygen consumption (VO_{2peak}) $<15 mL \cdot kg^{-1} \cdot min^{-1}$ appears to be a better predictor of post-operative complications than resting cardiac and pulmonary function (191, 195). Notably, this measurement was collected in a small number of facilities (i.e. 12%).

The benefit of providing physiotherapy for patients prior to thoracic surgery is unclear. Educating patients before their surgery about the post-operative physiotherapy management appears to have no effect on the incidence of post-operative pulmonary complications (272). Nevertheless, our data suggest that 44% of the respondents provided pre-operative education with respect to post-operative physiotherapy management.

The evidence for implementing physiotherapy treatment for patients prior to thoracic surgery is limited. Specifically, in patients awaiting surgery for lung cancer, Pehlivan et al (33) demonstrated that a one-week package of physiotherapy treatment comprising breathing and coughing exercises as well as treadmill walking reduced the incidence of post-operative pulmonary complications (from 17% to 3%) and length of hospital stay (from 9.7 to 5.4 days) of patients with lung cancer compared with a control group that did not receive any pre-operative physiotherapy. Although the study design precluded the determination of which physiotherapy intervention was responsible for the between-group differences, it is likely that treadmill walking was an important factor contributing to these results. That is, pre-operative exercise training has been consistently shown to optimise exercise capacity in patients with lung cancer (9, 273, 274) and this may serve to minimise the incidence of post-operative pulmonary complications. Although implementing a programme of high-intensity exercise may be advantageous in this population, our data indicate that such services are offered by very few hospitals; data that concurs with the findings of an earlier survey (37). Referrals to such programmes are likely to remain low, due at least in part to the fact that patients would like their cancer to be removed as soon as possible (32), and delaying surgery by a few weeks until a programme of exercise training has been completed is unacceptable. Nevertheless, perhaps there is a role for pre-operative exercise training for those who have resectable tumours but are not eligible for surgery due to their poor exercise capacity.

4.3.2 Post-operative management

Early mobilisation and the use of upright position are established as best practice in the management of patients following major abdominal, cardiac or thoracic surgery (275). In keeping with this, most of the respondents reported early mobilisation and

walking exercises as common post-operative treatments. The role of adding physiotherapy techniques, such as deep breathing exercises, to a programme of early mobilisation to minimise the incidence of post-operative pulmonary complications is controversial. A systematic review (276) of 35 studies (13 randomised controlled trials [RCTs]) concluded that there was little evidence for the effectiveness of respiratory physiotherapy in the prevention of pneumonia after abdominal surgery. Since this review, two high quality RCTs (34, 277) have explored the effect adding deep breathing exercises to a programme of early mobilisation following abdominal and thoracic surgeries. Neither study demonstrated an effect on preventing pulmonary complications. Nevertheless, it is important to note that the incidence of post-operative pulmonary complications and length of hospital stay in these two studies were both very low and thus the opportunity to confer a significant effect was limited. It is possible that such interventions are most appropriate for those who develop a post-operative pulmonary complication or have limited capacity to participate in early mobilisation. Our study suggests that most physiotherapists continue to implement breathing exercises frequently. This practice is likely to reflect a strong historical precedent for this treatment and is reflected in our data demonstrating that the single greatest influence on physiotherapists' choice of treatment was the established practice at their hospitals and personal experience.

In addition to minimising the incidence of post-operative pulmonary complications, the physiotherapist plays an integral role in restoring the patient to their pre-operative functional status. Evidence from a recent RCT (278) demonstrated that a post-operative programme of shoulder exercises improved shoulder function and decreased pain following open thoracotomy. Such a programme has yet to be implemented consistently given that only 24% of the respondents mentioned shoulder range of motion and thoracic range of movement exercises as techniques undertaken by the physiotherapists.

A low proportion of referrals to exercise training programmes after discharge were demonstrated by the current study. This may be due to both the lack of RCTs of supervised exercise training following discharge from hospital after resection for lung cancer as well as the fact that pulmonary rehabilitation programmes focus on patients with respiratory conditions other than lung cancer. Nevertheless, over the

past 6 years, several studies have been conducted to investigate the role of supervised exercise training for patients after surgery for lung cancer (28-31). They have demonstrated that exercise training is safe, feasible and may confer benefits on exercise capacity and HRQoL. To date, one RCT has investigated the effects of exercise following surgical resection for lung cancer. In this study the intervention group received twice daily strength and mobility training for the first 5 days after surgery followed by an additional 12 weeks of unsupervised home-based exercise (36). The control group received usual care which included airway clearance techniques, early ambulation and pain medication. The results showed that exercise assisted with maintaining quadriceps muscle force during the immediate post-operative period but was not associated with additional benefits in exercise capacity or HRQoL when re-assessed 12 weeks following discharge. An important limitation of this study was the relatively minimal interaction with a healthcare professional during the home exercise programme (i.e., once a month over the 3 month programme) as well as the lack of standardisation of the home exercises (i.e. they were individualised according to patient hobbies). Further RCTs are being performed to ascertain the effects of exercise training following surgery (279).

Strengths and limitations

The limitations of this study relate to those inherent within any survey of responder and recall bias. Our response rate of 91% suggests minimal responder bias. Further, inaccuracies related to recall bias were limited by; (i) ensuring that the questionnaire went to the physiotherapist who most frequently treated patients with lung cancer, (ii) instructing the respondents consult with other members of the healthcare team if they were unsure of the correct response and, (iii) following up with a phone call to address any perceived ambiguities in the questionnaire. For individual treatment approaches (e.g. walking-based exercise), we did not attempt to elicit specific prescription details such as frequency, intensity or duration as we believed these variables were likely to vary considerably between patients within any given hospital.

4.4 Conclusions

This study has documented current physiotherapy practice patterns for patients with lung cancer undergoing surgical resection throughout Australia and New Zealand and has demonstrated that physiotherapy services currently focus on minimising the immediate risk of post-operative pulmonary complications. Referral to exercise training is uncommon for this patient population and well-designed studies are needed to confirm the role of supervised exercise training in facilitating post-operative recovery in this patient population.

CHAPTER 5

OUTCOMES FOLLOWING CURATIVE INTENT TREATMENT FOR NON-SMALL CELL LUNG CANCER: A COMPARISON WITH AGE AND GENDER MATCHED HEALTHY CONTROLS

Overview

In this Chapter, outcomes such as exercise capacity, health-related quality of life (HRQoL), peripheral muscle force, physical activity, lung function and feelings of anxiety and depression measured in people following curative intent treatment (lobectomy with or without adjuvant chemotherapy) for non-small cell lung cancer (NSCLC) are compared with those collected in age and gender-matched healthy controls. The details of the study design are provided, including a description of participant inclusion and exclusion criteria and recruitment strategies. The assessment protocol and measurements made are described. For some participants with NSCLC, the data presented in this Chapter represent the baseline measures made as part of the randomised controlled trial that is presented in Chapter 8. Details of the statistical analyses used to compare people with NSCLC with age and gender-matched healthy controls are presented. The results of these analyses are provided and discussed.

The specific question answered in this Chapter is: Compared with age and gender-matched healthy controls, are measures of exercise capacity, HRQoL, peripheral muscle force, physical activity, lung function and feelings of anxiety and depression impaired in people following curative intent treatment for NSCLC?

The hypothesis was that, compared to age and gender-matched healthy controls, all outcomes will be impaired in those who have completed curative intent treatment for NSCLC.

5.1 Study design and methods

Overview

This study was cross-sectional and observational in design. Data collection was undertaken between February 2012 and April 2014. Measurements were collected of exercise capacity, HRQoL, peripheral muscle force, physical activity, lung function and feelings of anxiety and depression in people 6 to 10 weeks after lobectomy for NSCLC or, for those who went onto receive chemotherapy, 4 to 8 weeks after their last cycle of chemotherapy, as well as in age and gender-matched healthy controls. Assessments were initiated after participants gave written informed consent and were undertaken over 2 or 3 days, with a minimum of 24 hours between two assessment days, over a period of 2 to 3 weeks.

5.1.1 Ethics approval

The study was approved by the Human Research Ethics Committees of Sir Charles Gairdner Hospital (approval number 2011/105), Royal Perth Hospital (RA- 11/033) and Curtin University (approval number HR 178/2011).

5.1.2 Participants

Two groups of participants were recruited. These were; (i) people diagnosed with stage I, II or IIIA NSCLC who had received curative intent treatment and, (ii) those who constituted healthy controls.

5.1.2.1 People with NSCLC

5.1.2.1.1 Inclusion criteria

People were eligible to participate in this study if that had a diagnosis of primary NSCLC (stage I, II or IIIA) and were 6 to 10 weeks following lobectomy or, for

those who required adjuvant chemotherapy following surgery, 4 to 8 weeks following their last cycle.

5.1.2.1.2 Exclusion criteria

Exclusion criteria comprised; (i) need for pneumonectomy, (ii) presence of any co-morbid condition thought to compromise participant safety during the assessments, (iii) severe neuromusculoskeletal limitations that would impact on the exercise measures, (iv) participation in a programme of supervised exercise training in the last 3 months and, (v) inability to understand spoken or written English.

5.1.2.1.3 Recruitment

People with NSCLC were recruited from outpatient clinics and from referrals to the exercise training programmes at Sir Charles Gairdner Hospital (SCGH) and Royal Perth Hospital (RPH) as well as from a private thoracic surgery clinic in Perth.

5.1.2.2 Healthy controls

5.1.2.2.1 Inclusion criteria

Perth residents, aged between 55 and 80 years, with normal lung function were eligible to participate in this study.

5.1.2.2.2 Exclusion criteria

Exclusion criteria comprised; (i) presence of any cardiac, neuromusculoskeletal condition thought to adversely influence performance during any of the assessments and, (ii) inability to understand spoken or written English.

5.1.2.2.3 Recruitment

A convenience sample of healthy controls was recruited via advertisements on Curtin FM (Curtin University radio station) and in the POST (a local newspaper). Stratified sampling was used to select healthy people who responded to the advertisements. Strata for age (55 to 60 yr; 61 to 70 yr and 71 to 80 yr) and gender were created. Subsequently, healthy controls were recruited according to: (i) the order in which they responded to the advertisements and, (ii) the proportion of participants in the

NSCLC group that fit in each stratum. This process ensured that participants in this group were of similar age and gender as those in the NSCLC group and the proportion of males and females in the healthy control group was the same as in the NSCLC group.

5.1.3 Protocol

A choice to undertake assessments, for those who required a lobectomy without adjuvant chemotherapy, 6 to 10 weeks following surgery was made following consultation with thoracic surgeons as this time period was expected to be sufficient to allow wound healing and resolution of post-operative pain. For those who required adjuvant chemotherapy following surgery, assessment took place 4 to 8 weeks following their last cycle, to allow for resolution of the adverse effects of chemotherapy (i.e. nausea).

The first and second assessment days took place at either SCGH or RPH. On the first day of assessments, participants performed two six-minute walk tests (6MWTs), completed questionnaires pertaining to HRQoL, symptoms of anxiety and depression and dyspnoea, had their handgrip force measured and were given two physical activity monitors to be worn over 7 consecutive days. Following this period of 7 days, participants returned for the second day of assessments that comprised lung function tests as well as a cardiopulmonary exercise test (CPET). The third assessment day comprised the measure of isometric quadriceps muscle torque and took place at Curtin University. As the university is approximately 15 km from either of the hospitals, participants were given the option to decline this assessment.

5.2 Measurements

5.2.1 Primary outcomes

5.2.1.1 Exercise capacity

5.2.1.1.1 Cardiopulmonary exercise test (CPET) (undertaken by NSCLC and healthy control participants)

A symptom-limited ramp cycle ergometry exercise test was be performed on an electronically braked bicycle ergometer (ER 900; Jaeger, Hoechberg, Germany) in accordance with published guidelines (72). For participants with NSCLC, the rate at which the work rate increased during the test was determined using an equation that considered age, height, gender, forced expiratory volume in one second (FEV_1) and single breath diffusing capacity for carbon monoxide (D_LCO) (280). This individualised approach for work rate increments was used to attain the recommended CPET duration of 8 to 12 minutes (72, 280, 281). Increments varied from 1 W every 12 seconds (i.e. 5 W per minute) to 1 W every 5 seconds (i.e. 12 W per minute). For the healthy control participants, increments varied from 1 W every 8 seconds (i.e. 7.5 W per minute) to 1 W every 3 seconds (i.e. 20 W per minute). The increments in work rate were based on the participants predicted maximum work rate (Wmax) (282) and chosen based on a 10-minute test duration (72, 280, 281). For instance, if the predicted Wmax was 100 W, 10 W per minute (i.e. 1 W every 6 seconds) was chosen as the work rate increment. The reference equation for Wmax takes into account participant's age, height, weight and gender (282).

Participants were required to rest on the bike for 3 minutes. They then cycled (between 50 and 60 revolutions per minute) without any resistance for another 3 minutes. After this time, the resistance on the bike progressively increased until symptom limitation. During the test, breath-by-breath measurements were collected of minute ventilation, breathing pattern and gas exchange (Medgraphics CardiO2; Medical Graphics Corporation, St Paul, MN, USA). Blood pressure was measured every 2 minutes by automated sphygmomanometry. Twelve-lead electrocardiography was used throughout the test and arterial oxygen saturation measured via pulse oximetry (SpO_2) was continuously monitored (Radical; Masimo

Corporation, Irvine, CA, USA). The modified BORG scale (0-10) (283) was used to quantify level of dyspnoea (BORGd) and leg fatigue (BORGf) prior to starting the test, each minute during the test, and on test completion.

Given the random variability observed in measures obtained using breath-by-breath analysis, measures of the peak rate of oxygen consumption (VO_{2peak}) and maximum minute ventilation (VEmax) collected during the CPET were averaged over the last 20 seconds of the test (72). This methodology is consistent with the American Thoracic Society (ATS)/American College of Chest Physicians (ACCP) recommendations (72) and earlier work (284, 285). The Wmax and measures of VO_{2peak} were expressed in absolute values and as a percentage of the predicted value in a healthy population (282). Anaerobic threshold (AT) was determined by the software (BreezeSuite™; Medical Graphics Corporation, St Paul, MN, USA) using the V-slope method (286) and expressed as a percentage of VO_{2peak}. Two investigators, including an experienced respiratory scientist, analysed the determination of the AT by the software and made adjustments, based on visual inspection of the carbon dioxide output plotted against the oxygen uptake, when necessary. Oxygen pulse (O_2 pulse) was calculated by dividing the VO_{2peak} by the maximal heart rate (HRmax) (72). Breathing reserve (BR), expressed as a percentage, was calculated as the maximum voluntary ventilation (MVV), measured during the lung function test (see subheading 5.2.2.1 Lung function), minus the VEmax, multiplied by 100 and divided by the MVV (i.e. BR = [MVV – VEmax]*100/MVV) (14, 40).

The gas analysers, oximeter and pneumotacograph were calibrated prior to every test with all other monitors and equipment calibrated at time intervals in accordance with the manufacturer's recommendations.

5.2.1.1.2 Six-minute walk test (6MWT) (undertaken by NSCLC and healthy control participants)

Functional exercise capacity was evaluated using the 6MWT, which was undertaken according to a protocol based on the ATS recommendations (77). The 6MWT was performed over a 45-m level straight course within an enclosed corridor. Standardised instructions were read to each participant prior to commencing the test

and standardised encouragement was given at the end of every minute. Also, at the end of every minute, measures were collected of heart rate (HR) (Polar a1 heart rate monitor; Polar Electro Oy, Kempele, Finland) and SpO_2 (finger sensor and handheld pulse oximeter, Rad-57; Masimo Corporation, Irvine, CA, USA).

Two tests, separated by a 30-minute rest period, were conducted and the best distance achieved (i.e. six-minute walk distance [6MWD]) was recorded as the test result. The modified BORG scale (283) was used to quantify level of dyspnoea and leg fatigue prior to starting the test and on test completion. Data of 6MWD were expressed in absolute values and as a percentage of the predicted value in a healthy population (196).

5.2.1.2 Health-related quality of life

5.2.1.2.1 Medical outcomes study short form 36 general health survey (SF-36) (collected in NSCLC and healthy control participants)

The SF-36 is a self-complete questionnaire which assesses generic HRQoL (287). It comprises two major components: physical (physical component score [PCS]) and mental (mental component score [MCS]). The PCS comprise four domains; physical functioning, physical role functioning, bodily pain and, general health. The MCS also comprises four domains; vitality, social functioning, emotional role functioning and, mental health. The responses to items in each component and each domain are weighted equally, summed, and transformed to a 0 to 100 scale. Higher scores represent better HRQoL. The SF-36 has been widely used and its reliability and validity has been documented in people with a range of conditions that includes hypertension, diabetes, chronic heart failure and chronic obstructive pulmonary disease (COPD) (204, 288, 289).

5.2.1.2.2 The functional assessment of cancer therapy – lung scale (FACT-L) version 4 (collected in NSCLC participants only – data reported in Chapter 8)

The FACT-L version 4 is a self-complete 36-item questionnaire (290). It comprises five subscales; physical well-being, social/family well-being, emotional well-being, functional well-being as well as a separate lung cancer subscale. The FACT-L score ranges between 0 and 136, with higher scores representing better HRQoL. Internal

consistency of the five FACT-L subscales ranges between 0.56 and 0.89 (203). Compared with the first version of this questionnaire, the latest version (i.e. version 4) is more responsive to change and has superior internal consistency and content validity (203).

5.2.1.2.3 The European organisation for research and treatment of cancer, quality of life questionnaire core 30 (EORTC QLQ-C30) version 3 (collected in NSCLC participants only – data reported in Chapter 8)

The EORTC QLQ-C30 comprises 15 scales (291). Five scales pertain to function (i.e. physical, role, emotional, cognitive, and social), three scales pertain to symptoms (i.e. fatigue, pain, and nausea), and there is also one global measure of health status. The remaining six scales are single-item scales that assess the following symptoms; dyspnoea, appetite loss, sleep disturbance, constipation and diarrhoea, and the perceived financial impact of the disease treatment. Each scale ranges between 0 and 100. The EORTC QLQ-C30 takes, on average, 12 minutes to complete. Higher scores indicate better HRQoL for the function and global health status scales. Conversely, for symptoms, higher scores indicate worse symptoms. The questionnaire also includes, as an additional page, the lung cancer subscale (the EORTC-LC13). This subscale addresses 13 symptoms specific to people with lung cancer such as cough, dyspnoea, haemoptysis and chest pain (202). The magnitude of change in EORTC-C30 scores can be interpreted as small (5-10 units), moderate (10-20 units) or large (>20 units) (292). Test-retest reliability for the scales of the EORTC QLQ-C30 has been demonstrated to range between 0.63 and 0.91 (293).

5.2.1.3 Peripheral muscle force

5.2.1.3.1 Isometric quadriceps torque and isometric handgrip force (undertaken by NSCLC and healthy control participants)

Maximal isometric torque of the quadriceps was measured in an upright seated position using the HUMAC NORM isokinetic dynamometer (CSMi; Stoughton, MA, USA). The dominant leg was chosen (i.e. informed by the participants by telling which foot they used to kick a ball) and participants were asked to perform five maximum contractions of the quadriceps at 60º of knee flexion. Each contraction was

separated by 60 seconds. The contraction that generated the highest torque, and was within 5% of another effort, was recorded as the test result. Measures were expressed in absolute values and as a percentage of the predicted value in a healthy population (294). The equipment was calibrated prior to every test in accordance with the manufacturer's recommendations.

Isometric handgrip force was measured using a hydraulic hand dynamometer (Jamar dynamometer; JA Preston Corporation; Jackson, MI, USA). Peak handgrip force was assessed bilaterally, with the elbow at 90° of flexion and the forearm and wrist in a neutral position. Measures were expressed in absolute values and as a percentage of the predicted value in a healthy population (295). The hand dynamometer was calibrated at time intervals in accordance with the manufacturer's recommendations.

5.2.1.4 Physical activity

Participants were asked to wear two activity monitors (i.e. the SenseWear Armband and the Stepwatch Activity Monitor) for 7 consecutive days, during waking hours. They were asked to simultaneously attach these two activity monitors as soon as they woke up each day and remove them during showering and swimming activities as well as to sleep.

5.2.1.4.1 SenseWear armband (SAB) (collected in NSCLC and healthy control participants)

The SAB (BodyMedia Inc., Pittsburgh, PA, USA) is a small, light and portable metabolic monitor which has been validated to estimate energy expenditure in people with chronic lung diseases as well as in other populations (229, 237-239). In addition to a tri-axial accelerometer, it also comprises three other sensors which detect; (i) heat flux, (ii) skin temperature and, (iii) galvanic skin response. The device is worn over the triceps brachii muscle bulk of the left arm. Specific software (SenseWear Professional 7.0; Bodymedia Inc., Pittsburgh, PA, USA) was used to integrate the data from each sensor in order estimate energy expenditure.

5.2.1.4.2 Stepwatch activity monitor (SAM) (collected in NSCLC and healthy control participants)

The SAM (Cyma Corporation, Seattle, WA, USA) is a small, light microprocessor-controlled motion sensor that responds to time, acceleration and position (296). It has been shown to accurately detect steps, regardless of walking speed and the use of a wheeled walker (235). The SAM is attached to the right ankle using a Velcro strap. It records steps every minute. As the number of steps provided by the SAM represents steps taken by the right leg, total step count was calculated by multiplying this number by 2. When programming the SAM, the participant's height was entered. Information on walking speed, range of speeds and leg motion is also required for programming the device. For all participants walking speed was set as "normal", range of speeds was set as "uses a moderate range of speed" and leg motion was set as "normal".

Physical activity data management

In people following curative intent treatment for NSCLC, there are no studies that have investigated the minimum number of days and hours per day an activity monitor need to be worn in order to reliably measure physical activity and sedentary behaviour. Earlier work in 52 elderly people (13 males and 39 females; 69 ± 7 yr) has shown that a minimum of 4 full days of data (i.e. ≥ 10 hours/day) is necessary to reliably predict 21 consecutive days of activity monitoring (intra-class correlation coefficient > 0.8) (297). Large epidemiological studies investigating patterns of sedentary behaviour and physical activity in different populations have also used the criterion of 4 full days for data to be included in the analysis (47, 298, 299). Further, studies have also reported that adults are less active and more sedentary during weekends than during week days (300, 301). Therefore, in the current study, a minimum of 4 full days of data (defined as ≥ 10 hours/day wearing the monitors), including one weekend day were required for participants' data to be included in analyses. Data collected over all days that met these criteria were averaged for analysis.

5.2.2 Secondary outcomes

5.2.2.1 Lung function

Lung function testing comprised measures made using spirometry (forced vital capacity [FVC] and slow vital capacity [SVC] manoeuvres), body plethysmography and diffusing capacity for carbon monoxide. The healthy controls only underwent the FVC manoeuvre and the MVV assessment. Measures of MVV and maximal respiratory pressures were also collected. Bronchodilator therapy was not administered prior to lung function testing. The Medgraphics Elite Series DX plethysmograph (Medical Graphics Corporation, St Paul, MN, USA) was used to assess lung function and the equipment was calibrated prior to every test in accordance with the manufacturer's recommendations. All the assessments were performed according to published guidelines on standardisation of lung function testing (302-305). Measurements were expressed in absolute values and, where possible, as a percentage of the predicted value in a healthy population (306-308).

5.2.2.2 Dyspnoea and fatigue

5.2.2.2.1 Modified medical research council dyspnoea scale (MMRC) (collected in NSCLC participants only)

Functional limitation resulting from dyspnoea was assessed by the MMRC dyspnoea scale (309, 310). This simple scale comprises five statements. The participant selects the statement which best reflects their level of limitation in activities of daily life due to breathlessness. The MMRC dyspnoea scale is a valid method of categorising people with chronic lung disease in terms of their functional disability (311).

5.2.2.2.2 Functional assessment of chronic illness therapy - fatigue subscale (FACIT-Fatigue) (collected in NSCLC participants only)

Fatigue was assessed using the FACIT-Fatigue (312). The FACIT-Fatigue has 13 items answered on a 5-point rating scale and is based on a 7-day recall period. Scores range between 0 and 52, with lower scores reflecting greater fatigue. The questionnaire has good reliability and validity based on analyses of people with cancer and rheumatoid arthritis (312, 313).

5.2.2.3 Feelings of anxiety and depression

5.2.2.3.1 The hospital anxiety and depression scale (HADS) (collected in NSCLC and healthy control participants)

Feelings of anxiety and depression measured using the HADS (314). The HADS has been used to measure depression and generalised anxiety among hospitalised people, people attending outpatient clinics as well as in community settings (315-317). It comprises 14 statements describing symptoms of depression (7 items) and anxiety (7 items). Response options for each question range from 0 to 3, with a total range score between 0 and 21 for the depression and anxiety subscales. Higher scores represent greater feelings of depression and/or anxiety. Scores ≤ 7 are considered normal, scores > 7 and < 11 are considered borderline abnormal and values ≥ 11 are suggestive of a likely clinical diagnosis of depression or anxiety (314).

5.3 Statistical analyses

5.3.1 Sample size calculation

Compared with healthy controls, a previous study demonstrated that people with mild COPD had an average reduction in VO_{2peak} of 0.36 $L \cdot min^{-1}$ (318). The standard deviation of VO_{2peak} measured in this earlier study was 0.55 $L \cdot min^{-1}$ in those with COPD and 0.59 $L \cdot min^{-1}$ in the healthy controls (318). Although many people with NSCLC are likely to also have COPD, a greater difference was expected between the two groups in this study as the systemic effects of cancer as well as its treatment are likely to increase the impairments in exercise capacity over and above those attributed to COPD. Using these published data, a sample size of 18 participants with NSCLC and 18 healthy controls were needed to detect a between-group difference in VO_{2peak} of 0.55 $L \cdot min^{-1}$ with a standard deviation of 0.57 $L \cdot min^{-1}$ ($\alpha = 0.05$, $1 - \beta = 0.8$).

5.3.2 Statistical analyses

Statistical analyses were performed using SPSS® (Statistical Package for Social Sciences, version 22.0 for Windows). The distribution of data was examined by graphical (frequency histograms and box plots) and statistical methods (Shapiro-

Wilk test). Between-group comparisons of continuous data were undertaken using independent-samples *t*-test. Pearson Chi-square was used for comparison of categorical data. Differences between groups are reported as mean difference (MD) and 95% confidence interval (CI). For those variables from primary functional assessments (exercise capacity, peripheral muscle force and physical activity) which differed significantly between the NSCLC group and healthy controls, data from the healthy controls were used to calculate the lower limit of normal (LLN). The LLN was defined as the 5th percentile in measures, that is, the value above which 95% of the values in the healthy control were situated (43, 44). The LLN was used to establish cut-offs for significant impairment so that the number of participants in the NSCLC group who had significant impairments in those specific variables could be determined. For all analyses, a p value ≤ 0.05 was considered significant. All data are expressed as mean ± SD unless otherwise stated.

5.4 Results

From February 2012 to April 2014, 96 people following curative intent treatment for NSCLC were screened to participate in this study, of whom 71% (n = 68) were eligible and approached. Of these 68 people, a total of 25 consented to participate (consent rate of 37%). The reasons for declining participation are outlined in Figure 5-1. Two of the 25 (8%) were withdrawn due to health issues not related to lung cancer. Specifically, one participant was diagnosed with a primary bowel cancer and the other participant chose not to disclose the nature of the health issue that led to his withdrawal (Figure 5-1). During the same time period, 32 healthy people expressed interest in the study after hearing the advertisement on Curtin FM. Stratified sampling was used to select the first 20 eligible healthy people who expressed an interest in participating, and those 20 people were included in the study. Twenty-three participants following curative intent treatment for NSCLC (NSCLC group) and 20 healthy controls were included in final analysis (Figure 5-1). Baseline characteristics of the two groups are presented in Table 5-1.

Thirteen participants (57%) in the NSCLC group were recruited from SCGH and 10 (43%) participants were recruited from RPH. Nine participants (39%) underwent left upper lobectomy, one (4%) underwent left lower lobectomy, six (26%) underwent a

right upper lobectomy, six (26%) underwent a right lower lobectomy and one participant (4%) underwent right middle lobectomy. The average time between lobectomy and the first day of assessment was 54 ± 17 days. Two participants (9%) received adjuvant chemotherapy. For these participants, the time lapse between the last cycle of adjuvant chemotherapy and first day of assessment was 28 and 55 days.

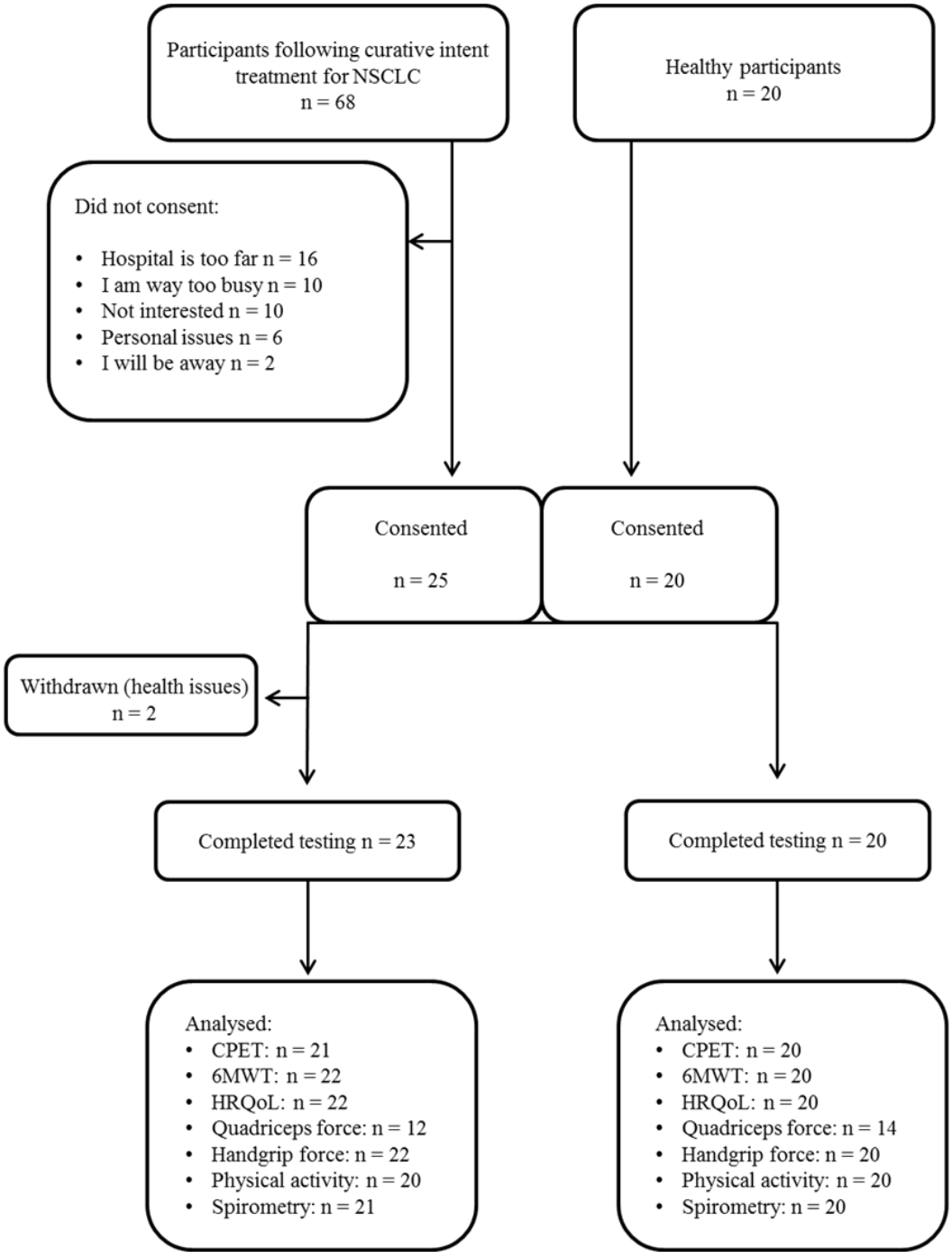

Figure 5-1: Study flow diagram

Abbreviations: 6MWT – Six-minute walk test; CPET – Cardiopulmonary exercise test; HRQoL – Health-related quality of life; NSCLC – Non-small cell lung cancer.

Table 5-1: Baseline characteristics

Variable	**NSCLC group (n=23)** *mean ± SD*		**Healthy Controls (n=20)** *mean ± SD*		***p value***
Age (yr)	68 ± 10		69 ± 5		*0.561*
Height (cm)	164 ± 12		167 ± 6		*< 0.001**
Weight (kg)	71 ± 21		71 ± 14		*< 0.001**
BMI ($kg \cdot m^{-2}$)	26 ± 6		25 ± 4		*0.756*
Smoking (pack/years)	39 ± 28		0.3 ± 0.9		*< 0.001**
FEV_1 (L)	1.65 ± 0.48		2.68 ± 0.54		*< 0.001**
FEV_1 (%pred)	67 ± 16		103 ± 15		*< 0.001**
FVC (L)	2.67 ± 0.71		3.44 ± 0.75		*< 0.001**
FVC (%pred)	81 ± 11		99 ± 15		*< 0.001**
	n	**%**	**n**	**%**	
Gender, male/female	7/16	30/70	7/13	35/65	*0.750*
Smoking status					
Current smoker	1	5	0	0	*0.345*
Ex-smoker	18	78	2	10	*< 0.001**
Never smoked	4	17	18	90	*< 0.001**
COPD	12	52	0	0	*< 0.001**
Other comorbidities					
Hypertension	13	57	2	10	*0.001**
Stable heart disease	4	17	1	5	*0.206*
Diabetes Mellitus	4	17	1	5	*0.206*
Dyslipidemia	5	22	6	30	*0.334*
GORD	3	13	1	5	*0.365*
Hypothyroidism	3	13	4	20	*0.538*
Other cancers (treated)	6	26	0	0	*< 0.001**
Type of NSCLC					
Adenocarcinoma	15	65			
Squamous cell carcinoma	7	30			
Large cell carcinoma	1	5			
NSCLC stage					
I	18	78			
II	3	13			
IIIA	2	9			
Type of surgery (lobectomy)					
Open	11	48			
VATS	12	52			
Adjuvant chemotherapy	2	9			

Abbreviations: BMI – Body-mass index; COPD – Chronic obstructive pulmonary disease; FEV_1 %pred – Forced expiratory volume in one second; GORD - Gastro-oesophageal reflux disease; MVV – Maximum voluntary ventilation; NSCLC – Non-small cell lung cancer; SD – Standard deviation; VATS – Video-assisted thoracoscopic surgery.
**Statistically significant difference between groups.*

5.4.1 Primary outcomes

5.4.1.1 Exercise capacity

5.4.1.1.1 Cardiopulmonary exercise test

The average duration of the CPET in the NSCLC group (9 ± 2 minutes) was similar to that in healthy controls (10 ± 2 minutes) ($p = 0.19$). The average work rate increment during the CPET was smaller for the NSCLC group than for the healthy controls (8 ± 2 *versus* 13 ± 4 W/min; $p < 0.001$). A comparison of the variables collected during the CPET between the two groups is presented in Table 5-2. Significant differences were observed in VO_{2peak},Wmax, nadir SpO_2, HRmax, BR, O_2 pulse and VEmax/MVV as well as dyspnoea measured on test completion. The LLNs calculated for VO_{2peak} and Wmax were 1.17 $L \cdot min^{-1}$ and 77 W, respectively. Fifteen of the 21 participants (71%) in the NSCLC group had a VO_{2peak} below the LLN. Regarding Wmax, 10 of 21 participants (48%) achieved a result below the LLN.

Regarding the symptoms that limited performance during the CPET, in the NSCLC group, eight participants (38%) were limited by dyspnoea, six (29%) were limited by leg fatigue, and seven (33%) were limited by a combination of dyspnoea and leg fatigue. For the healthy controls, four participants (20%) were limited by dyspnoea, 14 (70%) were limited by leg fatigue and two (10%) were limited by a combination of dyspnoea and leg fatigue. These proportions were significantly different between groups ($p = 0.03$).

5.4.1.1.2 Six-minute walk test

A comparison of variables collected during the 6MWT between the groups is presented in Table 5-2. Significant differences were observed in 6MWD, nadir SpO_2, peak HR as well as dyspnoea and leg fatigue measured on test completion. The LLN calculated for the 6MWD was 496 m. Ten of 22 participants (45%) in the NSCLC group had a 6MWD below the LLN (Table 5-2).

Table 5-2: Comparison of exercise capacity results between groups

Variable	**NSCLC group** *mean ± SD*	**Healthy Controls** *mean ± SD*	**Mean difference (MD)** *MD [95% CI]*	***p value***
CPET	***n = 21***	***n = 20***		
VO_{2peak} ($L \cdot min^{-1}$)	1.03 ± 0.31	1.69 ± 0.63	-0.65 [-0.96 to -0.34]	*< 0.001**
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	15 ± 3	24 ± 7	-8.7 [-12.1 to -5.3]	*< 0.001**
VO_{2peak} (%pred)	64 ± 15	95 ± 23	-32 [-44 to -19]	*< 0.001**
Wmax (W)	75 ± 25	127 ± 51	-52 [-77 to -26]	*< 0.001**
Wmax (%pred)	74 ± 20	122 ± 41	-48 [-69 to -28]	*< 0.001**
BORGd on completion CPET	6.9 ± 2.5	4.6 ± 1.8	2.3 [0.9 to 3.6]	*0.002**
BORGf on completion CPET	6.9 ± 2.4	6.3 ± 2.2	0.6 [-0.9 to 2.0]	*0.443*
Nadir SpO_2 (%)	94 ± 4	96 ± 2	-3 [-5 to -1]	*0.013**
HRmax (bpm)	129 ± 18	149 ± 12	-20 [-29 to -10]	*< 0.001**
BR (%)	31 ± 16	48 ± 12	-17 [-26 to -8]	*< 0.001**
O_2 pulse ($ml \cdot beat^{-1}$)	8 ± 3	11 ± 4	-3 [-5 to -1]	*0.004**
AT (%VO_{2peak})	62 ± 9	60 ± 6	-1.3 [-3.7 to -6.3]	*0.601*
VEmax/MVV (%)	69 ± 16	51 ± 12	18 [9 to 27]	*< 0.001**
6MWT	***n = 22***	***n = 20***		
6MWD (m)	494 ± 77	649 ± 61	-155 [-199 to -111]	*< 0.001**
6MWD (%pred)	80 ± 11	104 ± 7	-24 [-29 to -18]	*< 0.001**
BORGd on completion 6MWT	3.2 ± 1.6	1.4 ± 0.9	1.7 [0.9 to 2.6]	*< 0.001**
BORGf on completion 6MWT	2.0 ± 1.9	0.9 ± 0.9	1.1 [0.1 to 2.0]	*0.025**
Nadir SpO_2 (%)	93 ± 3	96 ± 1	-3 [-5 to -2]	*< 0.001**
Peak HR (bpm)	119 ± 14	137 ± 13	-18 [-27 to -10]	*< 0.001**

Abbreviations: 6MWT – Six-minute walk test; AT – Anaerobic threshold as a percentage of the VO_{2peak}; BORGd – Dyspnoea; BORGf – Fatigue; BR – Breathing reserve; CI – Confidence interval; CPET – Cardiopulmonary exercise test; HR – Heart rate; HRmax – Maximal heart rate; O_2 pulse – Oxygen pulse; SD – Standard deviation; SpO_2 - Arterial oxygen saturation measured via pulse oximetry; VEmax/MVV – Maximum minute ventilation, maximum voluntary ventilation ratio; VO_{2peak} – Peak rate of oxygen consumption; Wmax – Maximum work rate.**Statistically significant difference between groups.*

5.4.1.2 Health-related quality of life

Compared to healthy controls, scores for both PCS and MCS of the SF-36 were lower in participants in the NSCLC group (Table 5-3). The MD [95% CI] between the groups was greater in the PCS (-11 [-15 to -8]) than in the MCS (-6 [-11 to -2]) (p = 0.001). Lower scores for all the eight domains were also demonstrated in the NSCLC group (Table 5-3).

5.4.1.3 Isometric quadriceps torque and isometric handgrip force

Only 12 of 23 (52%) participants in the NSCLC group and 14 of 20 (70%) healthy controls attended Curtin University to undergo the measurement of isometric quadriceps torque (Figure 5-1). No between-group difference was demonstrated in isometric quadriceps torque expressed as absolute values (128 ± 64 [NSCLC group] *versus* 120 ± 40 Nm [healthy controls]; p = 0.68) (Figure 5-2) or as a percentage of the predicted values (97 ± 19% [NSCLC group] *versus* 104 ± 17 % [healthy controls]; p = 0.43).

The isometric handgrip force of participants in the NSCLC group was lower than the isometric handgrip force of healthy controls expressed as absolute values (28 ± 7 *versus* 34 ± 10 kg; p = 0.02) and as a percentage of the predicted values (101 ± 20% [NSCLC group] *versus* 123 ± 21% [healthy controls]; p = 0.001) (Figure 5-2).The LLN calculated for isometric handgrip force was 22 kg. Five of 22 participants (23%) in the NSCLC group had isometric handgrip force below the LLN.

Table 5-3: Comparison of health-related quality of life (SF-36) results between groups

Variable	**NSCLC group (n=22)** *mean ± SD*	**Healthy Controls (n=20)** *mean ± SD*	**Mean difference (MD)** *MD [95% CI]*	***p value***
PCS	45 ± 5	56 ± 5	-11 [-15 to -8]	*< 0.001**
MCS	51 ± 8	57 ± 7	-6 [-11 to -2]	*0.008**
Physical functioning	62 ± 19	93 ± 8	-31 [-41 to -22]	*< 0.001**
Role physical	60 ± 22	94 ± 9	-34 [-45 to -23]	*< 0.001**
Bodily pain	62 ± 19	81 ± 15	-19 [-29 to -8]	*0.001**
General health	67 ± 18	91 ± 9	-24 [-33 to -15]	*< 0.001**
Vitality	60 ± 18	77 ± 13	-17 [-27 to -7]	*0.001**
Social functioning	76 ± 21	94 ± 12	-19 [-30 to -8]	*< 0.001**
Role emotional	73 ± 23	95 ± 12	-22 [-33 to -10]	*< 0.001**
Mental health	75 ± 16	89 ± 12	-14 [-22 to -5]	*0.003**

Abbreviations: CI – Confidence interval; MCS – Mental component score; NSCLC – Non-small cell lung cancer; PCS – Physical component score; SD – Standard deviation.
**Statistically significant difference between groups.*

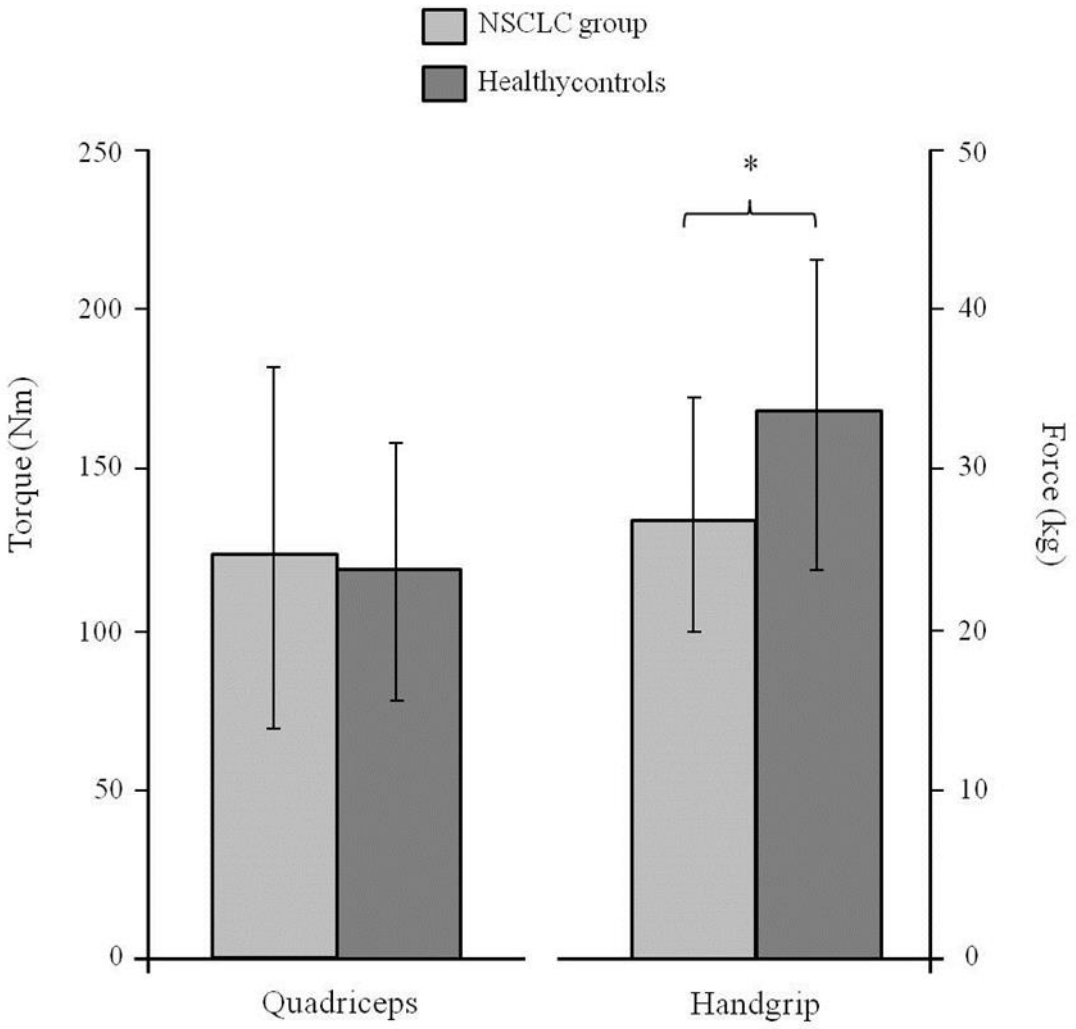

Figure 5-2: Comparison of isometric quadriceps torque and isometric handgrip force between groups. Data are mean ± standard deviation.

*p = 0.02

5.4.1.4 Physical activity

Of the 23 participants in the NSCLC group, one (4%) refused to wear both activity monitors and data from another two (9%) participants were not included as the SAB data file was corrupted (n = 1) and there was insufficient wear time (n = 1). Of the 20 participants in the NSCLC group who had their physical activity data analysed, 15 (75%) wore the activity monitors for ≥ 10 hours/day for all 7 days, four (20%) wore the monitors for ≥ 10 hours/day for 6 days and one (5%) wore the monitors for ≥ 10 hours/day for 5 days. Data collected for all 20 healthy controls were included in the analysis. Of these, 15 (75%) wore the activity monitors for ≥ 10 hours/day for all 7 days, four (20%) wore the monitors for ≥ 10 hours/day for 6 days and one (5%) wore the monitors for ≥ 10 hours/day for 5 days. There was no between-group difference in the number of hours per day that the monitors were worn (13.7 ± 1.2 hours/day [NSCLC group] *versus* 14.1 ± 0.9 hours/day [healthy controls]; $p = 0.21$).

5.4.1.4.1 SenseWear Armband

Time spent in moderate-to-vigorous intensity physical activity (i.e. activities that require an energy expenditure > 3 metabolic equivalent units [METs]) measured using the SAB was similar between the groups (94 ± 88 minutes/day [NSCLC group] *versus* 102 ± 98 minutes/day [healthy controls]; $p = 0.79$).

5.4.1.4.2 Stepwatch Activity Monitor

Average daily steps measured by the SAM was lower in the NSCLC group (8,863 ± 3,737 steps/day) compared with healthy controls (11,856 ± 3,024 steps/day) ($p = 0.009$). The calculated LLN for daily steps was 6,673 steps/day. Six of 20 participants (30%) in the NSCLC group had daily steps below the LLN. More detailed data on physical activity are presented in Chapter 6.

5.4.2 Secondary outcomes (lung function and feelings of anxiety and depression)

Comparisons of both lung function variables and feelings of anxiety and depression between the two groups are presented in Table 5-4. Significant differences were observed in all lung function variables. The depression component of the HADS was higher in the NSCLC group. Mean scores for both anxiety and depression

components of the HADS of participants in the NSCLC and healthy control groups were below the threshold used to suspect anxiety or depression. Only one participant in the NSCLC group had a score > 7 for anxiety and the same participant also had a score > 7 for depression. Two healthy controls had a score > 7 for anxiety, however depression scores were all within normal limits (i.e. ≤ 7).

Table 5-4: Comparison of lung function and levels of anxiety and depression between groups

Variable	**NSCLC group** *mean ± SD*	**Healthy Controls** *mean ± SD*	**Mean difference (MD)** *MD [95% CI]*	***p value***
Lung function	***n = 21***	***n = 20***		
FEV_1 (L)	1.6 ± 0.5	2.7 ± 0.5	-1.0 [-1.3 to -0.7]	*< 0.001**
FEV_1 (%pred)	67 ± 16	103 ± 15	-36 [-46 to -26]	*< 0.001**
FVC (L)	2.7 ± 0.7	3.5 ± 0.7	-0.8 [-1.2 to -0.3]	*0.001**
FVC (%pred)	81 ± 11	99 ± 15	-19 [-27 to -11]	*< 0.001**
FEV_1/FVC (%)	63 ± 12	78 ± 6	-15 [-21 to -9]	*< 0.001**
MVV ($L \cdot min^{-1}$)	63 ± 23	120 ± 31	-56 [-73 to -39]	*< 0.001**
MVV (%pred)	66 ± 19	119 ± 16	-53 [-64 to -42]	*< 0.001**
HADS	***n = 22***	***n = 20***		
Anxiety score	4.1 ± 2.4	2.9 ± 2.5	1.2 [-0.3 to 2.8]	*0.112*
Depression score	3.0 ± 2.5	1.5 ± 1.6	1.5 [0.2 to 2.9]	*0.026**

Abbreviations: CI – Confidence interval; FEV_1 – Forced expiratory volume in one second; FVC – Forced vital capacity; HADS – Hospital anxiety and depression scale; MVV – Maximum voluntary ventilation; SD – Standard deviation.
**Statistically significant difference between groups*

5.5 Discussion

This study has demonstrated that, on average, compared to age and gender-matched healthy controls, people following curative intent treatment for NSCLC demonstrate impairments in exercise capacity, HRQoL, isometric handgrip force and lung function and also take fewer steps each day. Conversely, following curative intent treatment for NSCLC, quadriceps torque, time spent in moderate-to-vigorous physical activity and feelings of anxiety and depression were similar to that measured in age and gender-matched healthy controls. Compared to previous studies that assessed outcomes in people following lung resection for NSCLC, this study was the first to include a broad range of outcomes measures and compare them with data collected in age and gender-matched healthy controls. This study was also the first to assess exercise capacity of people following lung resection for NSCLC using both a laboratory-based (CPET) and a field-based exercise test (6MWT).

5.5.1 Exercise capacity following curative intent treatment for NSCLC

5.5.1.1 Cardiopulmonary exercise test

The VO_{2peak} and Wmax of participants in the NSCLC group (15 $ml \cdot kg^{-1} \cdot min^{-1}$ and 75 W, respectively) were similar to that reported in other two studies (14, 69). The novel finding of this study was that following curative intent treatment for NSCLC, VO_{2peak} and Wmax were decreased by 38% and 39%, respectively, when compared with data collected in healthy controls. The Wmax achieved during a CPET, but not the VO_{2peak}, has been shown to be dependent on the work rate increment used during the test (319). Therefore, the magnitude of difference in Wmax (39%) is likely to have been influenced by the greater work rate increment used in the healthy controls. However, the CPET protocol used in the current study ensured an optimal test duration (i.e. between 8 and 12 minutes) (72) in both groups (9 ± 2 minutes [NSCLC group] and 10 ± 2 minutes [healthy controls]; $p = 0.19$). This optimal test duration might have minimised the influence of differences in work rate increments. Importantly, more than two-thirds (71%) of participants following curative intent treatment for NSCLC had decreased maximal exercise capacity (i.e. VO_{2peak} < LLN). These novel findings highlight the need for interventions that aim to increase

maximal exercise capacity in this population. This may be particularly important given that VO_{2peak} has been shown to be an independent predictor of mortality in people with NSCLC (194).

Regarding the symptom that limited performance during the CPET, the majority of participants in the NSCLC group (15 of 21 [71%]) stopped cycling due to either dyspnoea or a combination of dyspnoea and leg fatigue. This percentage seems to be greater than what was demonstrated in a previous study (40). That is, Wang et al (40) assessed 19 people following lobectomy for NSCLC and, although the researchers did not use a scale to quantify dyspnoea and leg fatigue on completion of the test, they reported that 10 participants (53%) stopped cycling due to either dyspnoea or a combination of dyspnoea and leg fatigue. A possible explanation for this discrepancy might be that participants from the current study had worse BR (31 ± 16%) and FEV_1 (67 ± 16% pred) than those from the study by Wang et al (36 ± 17% and 76 ± 15% pred, respectively) (40). That is, participants from the current study had greater ventilatory limitation during maximal exercise and thus reported higher levels of dyspnoea on completion of the CPET. This greater ventilatory limitation during the CPET may also explain the fact that, compared to healthy controls, a greater percentage of people in the NSCLC group stopped cycling due to dyspnoea (38 *versus* 20%; $p = 0.003$).

5.5.1.2 Six-minute walk test

The average 6MWD of participants in the NSCLC group (494 ± 77 m) was similar to what has been reported in a previous study (506 ± 95 m) (201). The novel information provided by this study is that people following curative intent treatment for NSCLC walked 155 m (24%) less than healthy controls (649 ± 61 m) in 6 minutes. Further, almost half of them achieved a 6MWD that was below the LLN. This is an important finding as the 6MWD is often used to detect changes in exercise capacity in people undergoing exercise training following lung resection for NSCLC and as a tool to prescribe walking training in this population (31, 320). This finding also corroborates the impairments in exercise capacity observed during the CPET. Given that exercise capacity was reduced in the NSCLC group, irrespective of the type of test used to assess this outcome (i.e. cycling and walking test), exercise

training programmes should consider including both cycling and walking in their training protocols for people following curative intent treatment for NSCLC. More detailed data on exercise capacity are presented in Chapter 7.

5.5.2 Health-related quality of life following curative intent treatment for NSCLC

The average scores of both the PCS and MCS as well as the average scores for most of the domains of the SF-36 of participants in the NSCLC group were slightly higher (i.e. better) than what has been reported in a previous study (321). These differences are likely to have occurred due to two main factors. The first factor is that, unlike the current study, the previous study comprised participants who had undergone lobectomy and participants who had undergone pneumonectomy. Of note, the literature has shown that people who undergo pneumonectomy present greater impairments in HRQoL than people who undergo lobectomy (209, 214). Second, compared to the current study, the previous study (321) had a greater percentage of participants who had received adjuvant chemotherapy (39% *versus* 10%). It is noteworthy that people who receive lung resection with adjuvant chemotherapy experience greater impairments in quality of life such as more vomiting, fatigue, loss of appetite and nausea than people who only undergo lung resection (322).

Impairments in HRQoL following curative intent treatment for NSCLC were demonstrated in this study. Compared to healthy controls, both the PCS and the MCS as well as all the physical and mental domains of the SF-36 were decreased in participants in the NSCLC group. Nevertheless, the MD [95% CI] between the two groups was greater in the PCS (-11 [-15 to -8]) than in the MCS (-6 [-11 to -2]) (p = 0.001). This finding suggests that people following curative intent treatment for NSCLC perceive that their HRQoL is more affected by physical issues than by mental or emotional issues. Accordingly, several studies have demonstrated a worsening of 14 to 19% in physical components of HRQoL up to 6 months following lung resection for NSCLC (41, 205, 206), whereas mental components of HRQoL have been shown to improve by approximately 10% between 3 to 6 months following lung resection (208-210). These findings highlight the importance of providing interventions aiming at improving physical function for people following

curative intent treatment for NSCLC. Exercise training is a potential intervention as it has been demonstrated to improve physical components of HRQoL in people with other lung diseases such as COPD (19) and idiopathic pulmonary fibrosis (20) as well as in survivors of cancer other than lung cancer (323). Although the Cochrane systematic review presented in Chapter 3 (106, 324) showed that exercise training has little effect on HRQoL of people following lung resection for NSCLC, the quality of the evidence was low and further investigation is required.

5.5.3 Isometric quadriceps torque and isometric handgrip force following curative intent treatment for NSCLC

The average isometric quadriceps torque of participants in the NSCLC group was 128 ± 64 Nm. No previous study in people following curative intent treatment for NSCLC has assessed quadriceps muscle torque using a similar protocol, thus comparisons with literature cannot be made. Participants in the NSCLC group had similar isometric quadriceps torque as the healthy controls. The study by Arbane et al (36) is the only previous study to investigate quadriceps force of people undergoing lung resection for NSCLC. Quadriceps force was assessed via magnetic stimulation of the femoral nerve in 25 people with NSCLC. The researchers demonstrated that there was no change in measures collected 12 weeks following lung resection (26.4 ± 9.7 kg) compared to those collected pre-operatively (29.1 ± 10.9 kg) ($p > 0.05$). However, of the 25 people with NSCLC who were assessed prior to lung resection in that study, only 13 (52%) returned for the 12-week assessment (36). This is a substantial attrition rate and it is possible that those people who returned for the 12-week assessment were not representative of the total sample. This is also likely to have occurred in the current study. That is, only 12 of the 23 participants (52%) in the NSCLC group attended Curtin University to undergo the measurement of isometric quadriceps muscle force. These participants might have been those with the least impairment and therefore, may not have been representative of the total NSCLC group.

This is the first study to measure isometric handgrip force specifically in people diagnosed with stage I, II or IIIA NSCLC (i.e. early stage NSCLC) and therefore there are limited data for comparison in the literature. Notwithstanding, muscle force

has been measured via hand dynamometry (handgrip) in people with advanced lung cancer (stage IIIB and IV) (246). Specifically, Brown et al (246) assessed 38 people (23 males) with advanced lung cancer (median [range] 64 [43 to 81] years) and demonstrated that their handgrip force was 22 (range: 7 to 51) kg. Therefore, on average, participants in the current study had a handgrip force that was 27% higher than people with advanced lung cancer. Despite being 27% stronger than people with advanced lung cancer, participants in the NSCLC group were 17% weaker than healthy controls (28 ± 7 *versus* 34 ± 10 kg; $p = 0.02$). Five of 22 participants (23%) of the current study had isometric handgrip force below the LLN calculated in healthy controls (22 kg). The relevance of this finding is that handgrip force is related to general muscle strength in older adults (325) and it is also a prognostic factor for mortality in middle-aged and elderly people (326). Although the effect that curative intent treatment for NSCLC has on peripheral muscle force needs further investigation, the measurement of handgrip force could add substantial information about general muscle strength. It could be easily incorporated during the baseline assessments for exercise training programmes as hand dynamometers are and easy to use as well as more affordable than isokinetic dynamometers.

5.5.4 Physical activity following curative intent treatment for NSCLC

The number of daily steps performed by the participants in the NSCLC group (8,863 ± 3,737 steps/day) was similar to that reported in people with mild COPD in two previous studies (7,960 ± 3,421 (243) and 7,960 ± 3,430 (327)) and twice as high as the number of daily steps reported in people with advanced NSCLC (4,246 ± 2,983 steps/day) (242). It is also consistent with the numbers of daily steps reported by the only previous study to investigate physical activity in people following lobectomy for NSCLC (241). Novoa et al (241) assessed physical activity of 18 people following lobectomy for NSCLC using a pedometer (OMROM Walking Style Pro). The study demonstrated that the mean number of daily steps during the 30 days after hospital discharge was 7,978 ± 4,486 steps/day. The outcome measure of physical activity of that study was limited to daily steps and the study did not have a comparison group of healthy controls. Of note, Novoa et al (241) reported a 25% decrease in daily steps from baseline (i.e. prior to lobectomy) to 30 days after hospital discharge following lobectomy.

Participants in the NSCLC group performed 25% less steps each day than healthy controls (8,863 ± 3,737 *versus* 11,856 ± 3,024 steps/day) ($p = 0.009$). Six of 20 participants (30%) in the NSCLC group had a daily step count below the LLN calculated in the healthy controls (6,673 steps/day). The present study also demonstrated that time spent in moderate-to-vigorous physical activity (measured by the SAB) was similar between the groups (94 ± 88 minutes/day [NSCLC group] *versus* 102 ± 98 minutes/day [healthy controls]; $p = 0.79$). Given that there was a significant difference in daily steps, but time in moderate-to-vigorous intensity physical activity was similar between the two groups, it is likely that people in the NSCLC group spent less time (or performed less steps) than healthy controls in physical activities that were not at moderate-to-vigorous intensity (i.e. light physical activities). This is discussed in depth in Chapter 6.

5.5.5 Lung function and feelings of anxiety and depression following curative intent treatment for NSCLC

5.5.5.1 Lung function following curative intent treatment for NSCLC

Data for lung function of participants in the NSCLC group are similar to values reported in previous studies (14, 38, 321). Not surprisingly, compared to healthy controls, all variables of lung function were decreased in participants in the NSCLC group. Lung function has consistently been shown to decrease after lung resection for NSCLC, regardless of the surgical technique (open thoracotomy or video-assisted thoracoscopic surgery) (189, 190). Measures such as the FEV_1 and FVC decrease following thoracic surgery and demonstrate limited recovery at 3 to 6 months after resection (38). Similar to people with chronic lung disease (93), the FEV_1 and FVC of people following lung resection for NSCLC do not change with exercise training (101, 106, 321, 324). Therefore, effectiveness of exercise training programmes in people following curative intent treatment for NSCLC should not be assessed using measures of lung function.

5.5.5.2 Feelings of anxiety and depression following curative intent treatment for NSCLC

This study demonstrated that feelings of anxiety and depression were within normal ranges (HADS anxiety and depression scores ≤ 7) in all but one participant in the NSCLC group. Despite these scores being normal following surgery, earlier work has shown that feelings of anxiety and depression are commonly experienced by people with NSCLC prior to lung resection (247). That is, prior to surgery, people fear death, loss of function, deformity and pain (247). However, at the time of hospital discharge following lung resection, feelings of anxiety and depression have been demonstrated to be significantly improved by 15 and 10%, respectively (247).

This is the first study to report that the anxiety score, measured via the HADS, of people following curative intent treatment for NSCLC was similar to that measured in healthy controls. Further, although there was a significant between-group difference in the depression score (3.0 ± 2.5 [NSCLC group] *versus* 1.5 ± 1.6 [healthy controls]; $p = 0.03$), the depression score of participants in the NSCLC group was ≤ 7 (i.e. considered normal). Importantly, these normal scores of anxiety and depression 2 months following lobectomy for NSCLC seem to last as long as 2 years (18). Myrdal et al (18), assessed 112 people 22 ± 12 months after lung resection for lung cancer also using the HADS. They demonstrated that the majority of individuals (75%) did not have scores that represented clinical anxiety or depression. The average scores for symptoms of anxiety and depression reported in this earlier study were 5.0 and 3.8, respectively (standard deviation was not reported) (18). Similar scores for anxiety were also reported by Granger et al (240), who followed 50 participants with stage IA to IIIB NSCLC from the time of diagnosis to 6 months following diagnosis. Half of the participants (25 of 50) underwent lung resection (with or without adjuvant chemotherapy) and the other 50% received either chemotherapy, radiotherapy or a combination of both. The study demonstrated no change in anxiety scores from baseline to 6 months (5.5 ± 0.7 *versus* 5.5 ± 0.7; $p = 0.94$) (240). Subgroup analysis comparing changes in the anxiety score of participants who underwent lung resection and those who did not undergo lung resection were not performed, precluding the comparison with findings from the present study.

Strengths and limitations

The main strengths of the current study were: (i) the assessment of exercise capacity using both a laboratory-based (CPET) and a field-based exercise test (6MWT); (ii) the investigation of the impact curative intent treatment for NSCLC has on a broad range of outcome measures; (iii) the comparison with healthy controls and, (iv) the use of stratified sampling to ensure that healthy controls and participants in the NSCLC group would be of similar age and gender. The main limitation of this study relates to the limited number of healthy controls to estimate the LLNs. These calculations may have been more robust if a larger sample were available. Nevertheless, in an earlier study which reported impairments in participants with cystic fibrosis the same number of healthy controls were used to derive measures of LLN (44). Another limitation of the current study was that people who underwent wedge resection or pneumonectomy for NSCLC were not included, thus the results cannot be extended to all people undergoing curative intent treatment for NSCLC. Finally, this study includes a large number of between-group comparisons which increases the risk of type I error. However, several comparisons, such as in measures of exercise capacity, HRQoL, isometric handgrip force, lung function and daily steps resulted in *p* values near 0.001 or even < 0.001. These *p* values suggest that type I error might have been minimised by the significant differences between participants in the NSCLC group and healthy controls in such measures.

5.6 Conclusions

Of the several outcomes measured, the greatest impairment detected in people following curative intent treatment for NSCLC, compared to healthy controls, was in exercise capacity. The magnitude of difference between groups in variables of exercise was large and 71% of participants following curative intent treatment for NSCLC presented decreased maximal exercise capacity (i.e. VO_{2peak} below the LLN). Compared to age and gender-matched healthy controls, people following curative intent treatment for NSCLC also demonstrated impairments in HRQoL, isometric handgrip force, lung function and daily steps. Conversely, quadriceps torque, time spent in moderate-to-vigorous physical activity and feelings of anxiety were similar to that measured in age and gender-matched healthy controls. Although

the depression score of people following curative intent treatment for NSCLC was higher than healthy controls, this score was within normal ranges.

These findings provide important information to clinicians working in the field. They highlight the need to refer people following curative intent treatment for NSCLC to exercise training programmes. As reported in the Cochrane review presented in Chapter 3, exercise capacity can be improved with exercise training (105, 106). However, as demonstrated in the survey presented in Chapter 4, referral to exercise training following lung resection for lung cancer is uncommon (248). The findings also highlight the need for further investigation on the impact curative intent treatment for NSCLC has on peripheral muscle force, given that handgrip force was reduced in the NSCLC group compared to healthy controls. Pertaining to measures of physical activity, future studies should consider looking for differences in activities other than those undertaken at a moderate-to-vigorous intensity. Further, the impairments demonstrated by participants following curative intent treatment for NSCLC in the current study emphasise that future research in exercise training for this group of people should focus on strategies to improve exercise capacity, HRQoL, peripheral muscle force and physical activity.

CHAPTER 6

PATTERNS OF SEDENTARY BEHAVIOUR AND PHYSICAL ACTIVITY FOLLOWING CURATIVE INTENT TREATMENT FOR NON-SMALL CELL LUNG CANCER

Overview

Data presented in Chapter 5 demonstrated that people following curative intent treatment for non-small cell lung cancer (NSCLC) had a lower daily step count than age and gender-matched healthy controls (8,863 ± 3,737 *versus* 11,856 ± 3,024 steps/day; $p = 0.009$). Nevertheless, the proportion of time spent in moderate-to-vigorous intensity physical activity was similar in both groups (94 ± 88 minutes/day [NSCLC group] *versus* 102 ± 98 minutes/day [healthy controls]; $p = 0.79$). This Chapter extends the analyses performed on these data by examining patterns of sedentary behaviour and physical activity in people following curative intent treatment for NSCLC and comparing these data with that collected in age and gender-matched healthy controls. That is, this Chapter compares the way sedentary behaviour and physical activity were accumulated in people following curative intent treatment for NSCLC and in age and gender-matched healthy controls. The devices used to measure sedentary behaviour and physical activity were described in Chapter 5 (heading 5.2 Measurements).

The specific question answered in this Chapter is: Do patterns of sedentary behaviour and physical activity of people following curative intent treatment for NSCLC differ from those in age and gender-matched healthy controls?

The first hypothesis was that, compared to age and gender-matched healthy people, people following curative intent treatment for NSCLC will spend a greater

percentage of waking hours in sedentary behaviour and a smaller percentage of waking hours being physically active. The second hypothesis was that, people following curative intent treatment for NSCLC will spend more time in prolonged, uninterrupted bouts of sedentary behaviour and less time in uninterrupted bouts of physical activity during waking hours compared with healthy controls.

6.1 Study design and methods

Overview

This study was cross-sectional and observational in design. Assessments completed by people following curative intent treatment for NSCLC (NSCLC group) were part of the baseline assessments for the randomised controlled trial that is presented in Chapter 8. Data collection was performed between February 2012 and April 2014 as described in Chapter 5 (heading 5.1.3 Protocol). Measurements were undertaken in people 6 to 10 weeks after lobectomy for NSCLC or, for those who required chemotherapy following surgery, 4 to 8 weeks after the last cycle of adjuvant chemotherapy as well as in age and gender-matched healthy controls. Assessments commenced after participants gave written, informed consent and were undertaken over one week.

6.1.1 Sedentary behaviour and physical activity

Sedentary behaviour and physical activity were assessed using the SenseWear armband (SAB) (BodyMedia Inc., Pittsburgh, PA, USA) and daily step count was assessed using the StepWatch activity monitor (SAM) (Cyma Corporation, Seattle, WA, USA) as described in Chapter 5 (heading 5.2.1.4 Physical activity).

The SAB is a small, light portable metabolic monitor which has been validated to estimate energy expenditure in healthy people, people with chronic lung diseases as well as in other populations (229, 237-239). The device is worn over the triceps brachii muscle bulk of the left arm. It provides minute-by-minute information on energy expenditure. The SAM is a small, light microprocessor-controlled motion sensor that responds to time, acceleration and position (296). It has been shown to accurately detect steps, regardless of walking speed or use of wheeled-walkers (235). It is worn on right ankle and attached using a Velcro strap. It records steps every

minute. Participants were asked to wear both the SAB and the SAM simultaneously for 7 consecutive days, throughout waking hours. They were instructed to remove the devices to sleep and during showering and swimming activities.

6.1.2 Data management

In people following curative intent treatment for NSCLC, there are no studies that have investigated the minimum number of days and hours per day an activity monitor needs to be worn in order to reliably measure physical activity and sedentary behaviour. The criteria used in the current study to define a minimum valid sample of activity monitoring was at least 4 full days of data (defined as ≥ 10 hours/day wearing the monitors), including one weekend day. The justification for these criteria has been presented in Chapter 5 (heading 5.2.1.4 Physical activity). Data collected over all days that met these criteria were averaged for analysis.

Data provided by the SAB were exported to Microsoft Excel™. Thereafter, a custom Labview programme (LabVIEW 8.6.1; National Instruments, Texas, USA) (328) was used to undertake exposure variation analysis (EVA). That is, using measures of METs derived from the SAB, the EVA calculated proportion of time spent in three domains: (i) sedentary behaviour (< 1.5 METs); (ii) light intensity physical activity (≥ 1.5 and < 3 METs) and; (iii) moderate-to-vigorous intensity physical activity (≥ 3 METs) (54). For each intensity domain, the EVA grouped data into time epochs. Given the recent research supporting the public health message of breaking up sedentary time every 30 minutes (63), time spent in sedentary behaviour was analysed in two epochs; 0 to < 30 minutes and ≥ 30 minutes. Given that the ACSM currently recommends that physical activity should be accumulated in bouts that exceed 10 minutes (54), time spent in light intensity physical activity and moderate-to-vigorous intensity physical activity was analysed in two epochs; 0 to < 10 minutes and ≥ 10 minutes. Data recorded using the SAM were exported to Microsoft Excel™. As the number of steps provided by the SAM represents steps taken by the right leg, total step count was calculated by multiplying this number by 2.

6.1.3 Statistical analysis

Statistical analyses were performed using SPSS® (Statistical Package for the Social Sciences, version 22.0 for Windows). The distribution of data was examined by graphical (frequency histograms and box plots) and statistical methods (Shapiro-Wilk test). Between-group comparisons were performed using either independent-samples *t*-test or the Mann-Whitney U test. Pearson Chi-square was used for comparison of categorical data. For all analyses, a p value ≤ 0.05 was considered significant. Data are expressed as mean ± standard deviation (SD) or median [interquartile range]. The EVA data are expressed in terms of time (minutes) and as percentages of total average daily wear time.

6.2 Results

The screening process for eligibility and inclusion of into the NSCLC and healthy control groups was detailed in Chapter 5 (Figure 5-1). Baseline characteristics of the two groups are presented in Table 6-1. Of the 23 participants in the NSCLC group, one (4%) refused to wear the SAM and data from other two (9%) participants were not included as the data file was corrupted (n = 1) and there was insufficient wear time (n = 1). Of the 20 participants in the NSCLC group who contributed data to the analyses presented in this Chapter, 15 (75%) wore the physical activity monitors for ≥ 10 hours/day for all 7 days, four (20%) wore the monitors for ≥ 10 hours/day for 6 days and one (5%) wore the monitors for ≥ 10 hours/day for 5 days. The average time lapse between the lobectomy and assessment of physical activity and sedentary behaviour was 55 ±18 days. Two participants (10%) received adjuvant chemotherapy. For these, the time lapse between the last cycle of adjuvant chemotherapy and the assessment of physical activity and sedentary behaviour was 28 and 55 days.

Data collected for all the 20 healthy controls were included in the analysis. Of these, 15 (75%) wore the physical activity monitors for ≥ 10 hours/day for all 7 days, four (20%) wore the monitors for ≥ 10 hours/day for 6 days and one (5%) wore the monitors for ≥ 10 hours/day for 5 days.

Table 6-1: Baseline characteristics

Variable	**NSCLC group (n=20)** *mean ± SD*		**Healthy Controls (n=20)** *mean ± SD*		***p value***
Age (yr)	68 ± 10		69 ± 5		*0.671*
Height (cm)	165 ± 13		167 ± 6		*0.356*
Weight (kg)	72 ± 21		71 ± 14		*0.823*
BMI ($kg \cdot m^{-2}$)	26 ± 6		25 ± 4		*0.789*
Smoking (pack/years)	35 ± 17		0.3 ± 0.9		*< 0.001**
FEV_1 (L)	1.69 ± 0.50		2.68 ± 0.54		*< 0.001**
FEV_1 (%pred)	67 ± 17		103 ± 15		*< 0.001**
FVC (L)	2.74 ± 0.74		3.44 ± 0.75		*< 0.001**
FVC (%pred)	81 ± 10		99 ± 15		*< 0.001**
	n	**%**	**n**	**%**	
Gender, male/female	7/13	35/65	7/13	35/65	*0.921*
Smoking status					
Current smoker	1	5	0	0	*0.345*
Ex-smoker	16	80	2	10	*< 0.001**
Never smoked	3	15	18	90	*< 0.001**
COPD	11	55	0	0	*< 0.001**
Other comorbidities					
Hypertension	11	55	2	10	*0.001**
Stable ischaemic heart disease	3	15	1	5	*0.249*
Diabetes Mellitus	3	15	1	5	*0.249*
Dyslipidemia	5	25	6	30	*0.385*
GORD	3	15	1	5	*0.392*
Hypothyroidism	2	10	3	15	*0.622*
Other cancers (treated)	6	30	0	0	*< 0.001**
Type of NSCLC					
Adenocarcinoma	14	70			
Squamous cell carcinoma	5	25			
Large cell carcinoma	1	5			
NSCLC stage					
I	15	75			
II	3	15			
IIIA	2	10			
Type of surgery (lobectomy)					
Open	8	40			
VATS	12	60			
Adjuvant chemotherapy	2	10			

Abbreviations: BMI: Body mass index; COPD – Chronic obstructive pulmonary disease; FEV_1 – Forced expiratory volume in one second; FVC – Forced vital capacity; GORD - Gastro-oesophageal reflux disease; MVV – Maximum voluntary ventilation; NSCLC – Non-small cell lung cancer; SD – Standard deviation; VATS – Video-assisted thoracoscopic surgery.
**Statistically significant difference between groups.*

6.2.1 Wear time

There was no between-group difference in number of days the monitors were worn (6.7 ± 0.6 days [NSCLC group] *versus* 6.7 ± 0.6 days [healthy controls]; $p = 0.83$), or in the average daily wear time (13.7 ± 1.2 hours/day [NSCLC group] *versus* 14.1 ± 0.9 hours/day [healthy controls]; $p = 0.27$).

6.2.2 Percentage of waking hours spent in sedentary behaviour, light and moderate-to-vigorous intensity physical activity

Figure 6-1 presents the percentage of time spent in sedentary behaviour, light and moderate-to-vigorous intensity physical activity in both groups. Compared with healthy controls, participants in the NSCLC group spent an additional 6 ± 19% of their waking hours in sedentary behaviour (62.0 ± 12.3% *versus* 68.0 ± 13.9% of waking hours, respectively). This was equivalent to 50 ± 187 additional minutes. However, this difference was not statistically significant ($p = 0.16$). Participants in the NSCLC group also spent 6 ± 11% less time, or 53 ± 85 minutes less, of their waking hours in light intensity physical activity than healthy controls (20.7 ± 9.0% *versus* 26.4 ± 7.8% of waking hours, respectively; $p = 0.04$). The percentage of waking hours spent in moderate-to-vigorous intensity physical activity was similar between the groups (11.3 ± 10.1% of waking hours [NSCLC group] *versus* 11.6 ± 10.7% of waking hours [healthy controls]; $p = 0.92$) (Figure 6-1).

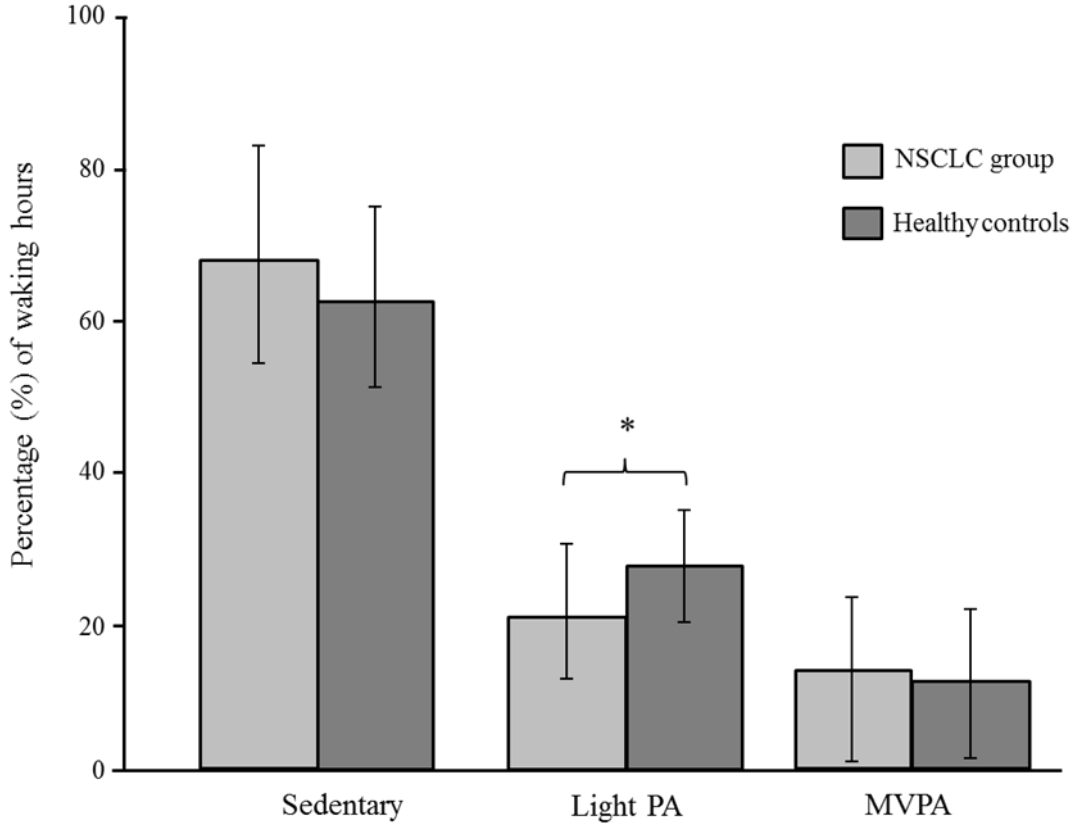

Figure 6-1: Comparison of the percentage of waking hours spent in sedentary behaviour, light intensity physical activity and moderate-to-vigorous intensity physical activity between groups. Data are expressed as mean ± standard deviation.

Abbreviations: MVPA – Moderate-to-vigorous intensity physical activity; PA – Physical activity.
*p = 0.04

6.2.3 Patterns of accumulation of sedentary behaviour and physical activity in bouts

For the NSCLC group and healthy controls, Table 6-2 presents the way in which time spent in sedentary behaviour, light and moderate-to-vigorous intensity physical activity were accumulated. Percentage of sedentary behaviour accumulated in uninterrupted bouts ≥ 30 minutes was 7% greater in the NSCLC group ($p = 0.048$). Percentage of light intensity physical activity accumulated in uninterrupted bouts ≥ 10 minutes was 6% lower in the NSCLC group ($p = 0.025$). No difference was found in the percentage of moderate-to-vigorous intensity physical activity accumulated uninterrupted bouts ≥ 10 minutes of between the groups ($p = 0.45$).

6.2.4 Daily step count

As reported in Chapter 5 (subheading 5.4.1.4 Physical activity), daily step count measured by the SAM was lower in the NSCLC group (8,863 ± 3,737 steps/day) compared with healthy controls (11,856 ± 3,024 steps/day) ($p = 0.009$).

Table 6-2: Patterns of accumulation of sedentary behaviour, light and moderate-to-vigorous intensity physical activity

Variables	**NSCLC group** n = 20	**Healthy controls** n = 20	***p value***
Percentage of time in sedentary behaviour in bouts ≥ 30 min	49 [42 to 65]	42 [30 to 58]	0.048*
Percentage of time in light intensity physical activity in bouts ≥ 10 min	13 [5 to 21]	19 [13 to 29]	0.025*
Percentage of time in moderate-to-vigorous physical activity in bouts ≥ 10 min	30 [17 to 40]	26 [13 to 50]	0.449

Data are expressed as median [interquartile range]. Abbreviation: NSCLC – Non-small cell lung cancer.
**Statistically significant difference between groups.*

6.3 Discussion

This is the first study to investigate patterns of sedentary behaviour and physical activity in people following curative intent treatment for NSCLC and compare these patterns with age and gender-matched healthy people. The results demonstrate that following curative intent treatment for NSCLC, people spent 68 ± 14%, 21 ± 9% and 11 ± 10% of their waking hours in sedentary behaviour, light intensity physical activity and moderate-to-vigorous intensity physical activity, respectively. Compared to healthy controls, participants in the NSCLC group spent a lower percentage of their waking hours in light intensity physical activity (6 ± 11%; $p = 0.04$). Further, participants in the NSCLC group accumulated a lower percentage of light intensity physical activity in uninterrupted bouts ≥ 10 minutes. Although the between-group difference in percentage of time in sedentary behaviour was not statistically significant (6 ± 19%; $p = 0.16$), people following curative intent treatment for NSCLC appeared to spend more time in sedentary behaviour at the expense of spending time in light intensity physical activity. Importantly, the percentage of time in sedentary behaviour accumulated in uninterrupted bouts ≥ 30 minutes was higher in the NSCLC group. No between-group differences were detected in the percentage of waking hours spent in moderate-to-vigorous intensity physical activity or in the way in which time in this domain was accumulated.

6.3.1 Sedentary behaviour

This is the first study to report data on sedentary behaviour in people following curative intent treatment for NSCLC. The current study demonstrated that this population spent 68 ± 14% of their waking hours in sedentary behaviour. Despite the lack of data in people with lung cancer, similar values of percentage of waking hours spent in sedentary behaviour have been published in people with breast and prostate cancer (329, 330). Using the Actigraph activity monitor (model 7164; LLC, Fort Walton Beach, Florida, USA) and a pragmatic cut-off of < 100 counts/min for sedentary behaviour, Lynch et al (329, 330) demonstrated that survivors of prostate (330) and breast cancer (329) spent 66 ± 12% and 69 ± 11% of their waking hours in sedentary behaviour, respectively. Further, women with a history of breast cancer spent on average 8% (i.e. 1 hour/day) more time in sedentary behaviour than gender-

matched healthy controls (329). This is in keeping with the result of the current study which showed that participants following lobectomy for NSCLC spent 6% more time (i.e. 50 min/day) in sedentary behaviour than healthy controls. However, this difference in time spent in sedentary behaviour between the NSCLC and healthy control groups did not reach statistical significance, presumably due to significant variability in this outcome measure and the small sample size of the study.

The way sedentary behaviour is accumulated is also important (47). A cross-sectional study on 4,757 healthy adults (47 ± 14 yr) has demonstrated that, regardless of the total time spent in sedentary behaviour, infrequent breaks in sedentary behaviour were detrimentally associated with waist circumference and level of C-reactive protein, which are markers of poor cardio-metabolic health (47). Although there is still no evidence pertaining to how often people should interrupt sedentary behaviours, a literature review published in 2011 proposed the idea of a public health message that sedentary behaviours should be interrupted every 30 minutes (63). Findings of the current study have shown that the percentage of time participants in the NSCLC group spent in prolonged, uninterrupted bouts ≥ 30 minutes of sedentary behaviour was higher than healthy controls. That is, breaks in sedentary behaviour were less frequent in the NSCLC group. This finding reinforces the importance of implementing interventions that aim at breaking up sedentary behaviour for people following curative intent treatment for NSCLC.

6.3.2 Light intensity physical activity

This is also the first study to report data on light intensity physical activity in people following curative intent treatment for NSCLC. In the current study, participants in the NSCLC group spent 21 ± 9% of their waking hours in light intensity physical activity. Despite the lack of data in people with lung cancer, previous studies have reported percentage of waking hours spent in light intensity physical of people with breast and prostate cancer (329, 330). Survivors of prostate and breast cancer have been shown to spend 27% and 33%, respectively, of their waking hours in this domain (329, 330). This modest discrepancy in light intensity physical activity data between the current study and the studies on survivors of prostate and breast cancer (329, 330) is likely to have been due to differences in the cut-offs chosen for light

intensity physical activity. That is, in the current study, the SAB was used to measure physical activity and the cut-off for light intensity physical activity was based on an energy expenditure ≥ 1.5 and < 3 METs (54). In the studies on survivors of prostate and breast cancer (329, 330), the Actigraph was used and a cut-off ≥ 100 to < 1,952 counts/min was chosen to define light intensity physical activity. However, this cut-off of ≥ 100 to < 1,952 counts/min was calculated and proposed by a study on a young adult population (25 ± 4 yr) (331). It is likely that a lower threshold would be more appropriate for an older population. Specifically, Swartz et al (332) compared the same model of the Actigraph with indirect calorimetry in order to determine cut-offs for light and moderate-to-vigorous intensity physical activity. The study included 70 participants (41 ± 15 yr) who performed six different daily activities and demonstrated that the cut-off for light intensity physical activity (i.e. energy expenditure ≥ 1.5 and < 3 METs) was ≥ 100 to < 574 counts/min. If this cut-off had been used in the studies on survivors of prostate and breast cancer (329, 330), percentage of time spent in light intensity physical activity would have been reduced to values similar to the current study.

The current study demonstrated that people in the NSCLC group spent 6% less time in light intensity physical activity than healthy controls. Likewise, women with breast cancer have been demonstrated to spend 7% less time in light intensity physical activity (329) than healthy controls. Further, compared with healthy controls, participants in the NSCLC group spent a smaller percentage of their waking hours in uninterrupted bouts ≥ 10 minutes of light intensity physical activity (2.3 [0.7 to 5.9]% [NSCLC group] *versus* 5.6 [2.7 to 7.3]% [healthy controls]; $p = 0.03$). These findings are relevant because time spent in light intensity physical activity has been shown to be associated with lower waist circumference, BMI, level of C-reactive protein and 2-hour fasting plasma glucose levels in the general population (48, 333). This association is independent of the time spent in moderate-to-vigorous intensity physical activity (48, 333). Of note, studies in healthy people as well as in people with breast and prostate cancer have demonstrated a strong inverse association between percentage of time spent in light intensity physical activity and percentage of time spent in sedentary behaviour (r = -0.96 to -0.99) (45, 329, 330). Therefore, interventions that aim to increase levels of light intensity physical activity by decreasing time in sedentary behaviour are important and may decrease the risk of

type-2 diabetes and cardiovascular disease in people following curative intent treatment for NSCLC (333).

6.3.3 Moderate-to-vigorous physical activity

Participants in the NSCLC group spent 11 ± 10% of their waking hours in moderate-to-vigorous intensity physical activity. This is more than what has been reported in survivors of prostate and breast cancer (4% and 1%, respectively) (329, 330). However, as previously discussed, these discrepancies are likely to have been due to differences in the cut-offs chosen for light intensity and moderate-to-vigorous intensity physical activity. In the previously mentioned studies that used the Actigraph to assess physical activity on survivors of prostate and breast cancer (329, 330), a cut-off ≥1,952 counts/min was chosen to define moderate-to-vigorous intensity physical activity. This cut-off was taken from a study on a young adult population (25 ± 4 yr) (331) and it is likely that a lower threshold would be more appropriate for an older population. Specifically, Swartz et al (332) demonstrated that the cut-off for moderate-to-vigorous intensity physical activity (i.e. energy expenditure ≥ 3 METs) on a population aged 41 ± 15 years was ≥ 574 counts/min. Therefore, percentage of time spent in moderate-to-vigorous intensity physical activity in the studies on survivors of prostate and breast cancer (329, 330) would have been higher and similar to values of the current study if the cut-off proposed by Swartz et al (≥ 574 counts/min) (332) had been used.

The current study also demonstrated that both the time spent in moderate-to-vigorous intensity physical activity and the percentage of waking hours accumulated in uninterrupted bouts ≥ 10 minutes of moderate-to-vigorous intensity physical activity were similar between the groups. However, daily step count measured by the SAM was lower by 3,000 steps per day in the NSCLC group. As time spent in moderate-to-vigorous intensity physical activity was similar between groups, this difference in daily steps is likely to have reflected a difference in time spent in light intensity physical activity. That is, it is likely that participants in the NSCLC group performed similar number of steps as the healthy controls during moderate-to-vigorous intensity activities and less steps than healthy people during light intensity physical activity.

These results reinforce the importance of interventions aiming at increasing light intensity physical activity in people following curative intent treatment for NSCLC.

Strengths and limitations

The main strengths of the current study were: (i) the investigation of sedentary behaviour in people following curative intent treatment for NSCLC; (ii) the analyses of time spent in both light and moderate-to-vigorous physical activity which went beyond the simple measure of daily steps and, (iii) reporting the way in which time in sedentary behaviour and physical activity were accumulated. Of note, data collected in the NSCLC groups were compared with data collected in age and gender-matched healthy controls. One of the limitations was the sample size of the study. A larger sample size would have afforded greater power to detect differences. We were also unable to determine the impact surgery had on sedentary behaviour and physical activity as data were not collected prior to surgery. Future studies should consider collecting longitudinal data, starting from a baseline assessment prior to surgery and following participants for a longer period after the curative intent treatment. Further, people who underwent wedge resection or pneumonectomy for NSCLC were not included in the study, thus the results cannot be extended to all people undergoing lung resection for NSCLC.

6.4 Conclusions

Although spending a similar proportion of time in moderate-to-vigorous intensity physical activity, participants in the NSCLC group spent considerably less time than healthy controls performing light intensity physical activity and significantly more time in prolonged uninterrupted bouts of sedentary behaviour. Strategies aiming at displacing time in sedentary behaviour with time in light intensity physical activity may improve health outcomes in people following curative intent treatment for NSCLC and warrants further investigation.

CHAPTER 7

EXERCISE RESPONSES DURING THE CARDIOPULMONARY EXERCISE TEST AND THE SIX-MINUTE WALK TEST FOLLOWING CURATIVE INTENT TREATMENT FOR NON-SMALL CELL LUNG CANCER

Overview

Data presented in Chapter 5 demonstrated that compared to age and gender-matched healthy controls, people following curative intent treatment for non-small cell lung cancer (NSCLC) had both decreased peak rate of oxygen consumption (VO_{2peak}) measured during the cardiopulmonary exercise test (CPET) (1.03 ± 0.31 [NSCLC group] *versus* 1.69 ± 0.63 [healthy controls] $L \cdot min^{-1}$; $p < 0.001$) and walked a shorter distance during the six-minute walk test (6MWT) (494 ± 77 [NSCLC group] *versus* 649 ± 61 [healthy controls] m; $p < 0.001$). This Chapter extends the analyses performed on the exercise test data by examining exercise responses as well as patterns of exercise responses during both the CPET and the 6MWT in people following lung resection for NSCLC.

The specific question answered in this Chapter is: Does the 6MWT elicit similar peak exercise responses and patterns of change in heart rate (HR) and arterial oxygen saturation measured via pulse oximetry (SpO_2) as the CPET in people following curative intent treatment for NSCLC?

The hypothesis was that the 6MWT will elicit similar peak exercise responses to the CPET, however the patterns of change in HR and SpO_2 during the 6MWT will not have the linear pattern commonly observed during the CPET. The methods used to conduct the exercise and lung function tests reported in this study have been

described in full in Chapter 5 (heading 5.2 Measurements). This Chapter presents an overview of the methodology for this study, describes the study participants and presents data pertaining to the comparison of peak exercise responses and patterns of change in HR and SpO_2 during the CPET and the 6MWT.

7.1 Study design and methods

Overview

This study was cross-sectional and observational in design. Assessments completed by people following curative intent treatment for NSCLC were part of the baseline assessments for the randomised controlled trial that is presented in Chapter 8. Data collection was performed between February 2012 and April 2014 as described in Chapter 5 (heading 5.1.3 Protocol). Measurements were undertaken in people 6 to 10 weeks after lobectomy for NSCLC or, for those who required chemotherapy, 4 to 8 weeks after the last cycle of adjuvant chemotherapy. Assessments commenced after participants gave written, informed consent and were undertaken over 2 weeks.

7.1.1 Exercise capacity measurements

The CPET and 6MWT were performed on different days that were separated by at least 7 days. On the first assessment day, exercise capacity was evaluated using the 6MWT, using a test protocol that was based on the American Thoracic Society (ATS) recommendations (77). The participants underwent two 6MWTs, separated by a 30-minute rest period. The 6MWT was performed over a 45-m level straight course within an enclosed corridor (77). Standardised encouragement was given at the end of every minute. Also, at the end of every minute measures were collected of heart rate (Polar a1 heart rate monitor; Polar Electro Oy, Kempele, Finland) and arterial oxygen saturation measured via pulse oximetry (SpO_2) (finger sensor and handheld pulse oximeter, Rad-57; Masimo Corporation, Irvine, CA, USA). The modified BORG scale (0-10) (283) was used to quantify level of dyspnoea (BORGd) prior to starting the test and on test completion and leg fatigue (BORGf) on test completion. The best six-minute walk distance (6MWD) was recorded as the test result. The 6MWD for each participant was expressed in absolute values and as a percentage of the predicted value in a healthy Australian population (196).

On the second assessment day, participants performed a symptom-limited ramp cycle ergometry exercise test on an electronically braked bicycle ergometer (ER 900; Jaeger, Hoechberg, Germany) using a protocol based on published guidelines (72). A single test was performed as studies in IPF and COPD have reported acceptable reproducibility of Wmax when two tests were performed (334, 335). During the test, breath-by-breath measurements were collected of ventilation, breathing pattern and gas exchange (Medgraphics CardiO2; Medical Graphics Corporation, St Paul, MN, USA). Blood pressure was measured every 2 minutes by automated sphygmomanometry. Twelve-lead electrocardiography was used throughout the test and SpO_2 was continuously monitored using a pulse oximeter (Radical, Masimo Corporation, Irvine, CA, USA). The modified BORG scale (283) was used to quantify level of dyspnoea and leg fatigue prior to starting the test, each minute during the test, and at test completion. Reference values developed by Blackie et al (282) were used to express VO_{2peak} and Wmax as a percentage of the predicted value for healthy adults. For full details on exercise capacity measurements refer to Chapter 5 (heading 5.2 Measurements).

7.1.2 Statistical analyses and data management

Statistical analyses were performed using SPSS® (Statistical Package for Social Sciences, version 22.0 for Windows) and SigmaPlot (version 12.0). The distribution of data was examined by graphical (frequency histograms and box plots) and statistical methods (Shapiro-Wilk test). The effect of familiarisation on 6MWD was examined using paired *t*-test. Significant oxygen desaturation during the 6MWT and CPET was defined as a > 4% fall in SpO_2 from resting measures, to a value < 90% (336). Peak HR, nadir SpO_2 and end-test BORGd and BORGf elicited during the two tests were compared using paired *t*-test. In order to compare the patterns of changes in measures of HR and SpO_2 during each test, data were grouped into deciles (i.e. epochs equivalent to 10% of the total test duration) using a two-dimensional data transformation. Comparison of both HR and SpO_2 at each decile throughout the 6MWT and the CPET was performed using one-way repeated measures analysis of variance with Tukey's post-hoc. For all analyses, a p value ≤ 0.05 was considered significant. Data are expressed as mean ± standard deviation (SD). Differences

between the exercise tests are expressed as mean difference (MD) [95% confidence interval (CI)].

7.2 Results

The screening process for eligibility and inclusion of people following curative intent treatment for NSCLC has been described in detail in Chapter 5 (Figure 5-1). Complete CPET and 6MWT data were available in 20 people following curative intent treatment for NSCLC. The average time lapse between the lobectomy and the first assessment day was 56 ± 18 days. Two participants (10%) received adjuvant chemotherapy. For these, the time lapse between the last cycle of adjuvant chemotherapy and first assessment day was 28 and 55 days. Characteristics of the participants are presented in Table 7-1.

Table 7-1: Characteristics of the 20 participants (14 female)

Variable	Mean ± SD	
Age (yr)	67 ± 10	
BMI ($kg \cdot m^{-2}$)	26 ± 6	
Smoking (pack/yr)	36 ± 26	
FEV_1 (L)	1.65 ± 0.49	
FEV_1 (%pred)	67 ± 16	
FVC (L)	2.69 ± 0.72	
FVC (%pred)	81 ± 11	
FEV_1/FVC	0.63 ± 0.12	
D_LCO ($ml \cdot mmHg^{-1} \cdot min^{-1}$)	13.6 ± 3.4	
D_LCO (%pred)	53 ± 11	
	n	**%**
Gender, male/female	6/14	30/70
Smoking status		
Ex-smoker	17	85
Never smoked	3	15
COPD	10	50
Other comorbidities		
Hypertension	11	55
Stable ischaemic heart disease	3	15
Diabetes mellitus	3	15
Dyslipidemia	4	20
GORD	3	15
Hypothyroidism	2	10
Other cancers (treated)	6	30
Type of NSCLC		
Adenocarcinoma	13	65
Squamous cell carcinoma	6	30
Large cell carcinoma	1	5
NSCLC stage		
I	16	80
II	3	15
IIIA	1	5
Type of surgery (lobectomy)		
Open	9	45
VATS	11	55
Adjuvant chemotherapy	1	5

Abbreviations: BMI – Body-mass index; COPD – Chronic obstructive pulmonary disease; D_LCO – Single breath diffusing capacity for carbon monoxide; FEV_1 – Forced expiratory volume in one second; FVC – Forced vital capacity; GORD - Gastro-oesophageal reflux disease; MVV – Maximum voluntary ventilation; NSCLC – Non-small cell lung cancer; SD – Standard deviation; VATS – Video-assisted thoracoscopic surgery.
*Defined by pre-operative $FEV_1/FVC < 0.70$ (337).

7.2.1 Cardiopulmonary exercise test

Results of the CPET are shown in Table 7.2.

7.2.1.1 Responses during the cardiopulmonary exercise test

Heart rate increased during the CPET from 85 ± 13 (resting heart rate) to 128 ± 18 bpm (peak heart rate) (variation [Δ] HR = 44 ± 16 bpm; $p < 0.001$). The SpO_2 during the CPET decreased from 97 ± 2 (resting SpO_2) to 95 ± 3% (nadir SpO_2) (ΔSpO_2 = -1 ± 3%; $p = 0.02$). One participant (5%) desaturated > 4% to a SpO_2 < 90% during the CPET. There was no difference between end-test BORGd (6.9 ± 2.6) and end-test BORGf (6.8 ± 2.4) (MD [95% CI]; 0.1 [-1.2 to 1.4]; $p = 0.87$). Regarding the symptoms that limited performance during the CPET, eight participants (40%) were limited by dyspnoea, five (25%) were limited by leg fatigue, and seven (35%) were limited by a combination of dyspnoea and leg fatigue.

7.2.2 Six-minute walk test

Results of the 6MWT are shown in Table 7-2. None of the participants required a rest during the 6MWT. Eighteen of the 20 participants (90%) increased their 6MWD on the second 6MWT. The increase in 6MWD on the second 6MWT was 19 ± 19 m or 4 ± 4% ($p < 0.001$).

7.2.2.1 Responses during the six-minute walk test

Heart rate increased during the 6MWT from 83 ± 10 (resting heart rate) to 119 ± 15 bpm (peak heart rate) (ΔHR = 37 ± 14 bpm; $p < 0.001$). The SpO_2 during the 6MWT decreased from 97 ± 1 (resting SpO_2) to 93 ± 3% (nadir SpO_2) (ΔSpO_2 = 4 ± 2%; $p < 0.001$). Two participants (10%) desaturated > 4% to a SpO_2 < 90% during the 6MWT. There was no difference between end-test BORGd (3.1 ± 1.6) and end-test BORGf (2.0 ± 1.9) (MD [95% CI]; 1.1 [-0.0 to 2]; $p = 0.06$).

Table 7-2: Results of the exercise tests

Variable	Mean ± SD (n = 20)
CPET	
Duration (min)	9.3 ± 1.6
VO_{2peak} ($L \cdot min^{-1}$)	1.03 ± 0.31
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	15 ± 3
VO_{2peak} (%pred)	63 ± 15
Wmax (W)	76 ± 26
Wmax (%pred)	72 ± 20
VEmax ($L \cdot min^{-1}$)	43 ± 15
VEmax/MVV (%)	70 ± 20
6MWT	
6MWD (m)	503 ± 71
6MWD (%pred)	81 ± 10

Abbreviations: 6MWD – Six-minute walk distance; 6MWT – Six-minute walk test; CPET – Cardiopulmonary exercise test; MVV – Maximum voluntary ventilation; VEmax – Maximum minute ventilation; VO_{2peak} – Peak rate of oxygen consumption; Wmax – Maximum work rate.

7.2.3 Comparison between exercise responses and patterns of exercise responses during the two exercise tests

7.2.3.1 Exercise responses

The comparison of resting HR, peak HR, ΔHR, resting SpO_2, nadir SpO_2, ΔSpO_2 and end-test symptoms during the 6MWT and CPET are presented in Table 7-3. Peak HR was higher during the CPET (MD [95% CI]; 9 [1 to 16] bpm; $p = 0.02$) however there was no difference in ΔHR between the CPET and 6MWT (MD [95% CI]; 7 [-15 to 1] bpm; $p = 0.10$). Both nadir SpO_2 and ΔSpO_2 were lower during the 6MWT (MD [95% CI] nadir SpO_2; -2 [-4 to -1]%; $p = 0.01$; MD [95% CI] ΔSpO_2; -2 [-4 to -1]%; $p < 0.01$ for both). People following curative intent treatment for NSCLC reported less dyspnoea and leg fatigue on completion of 6MWT compared to the CPET (MD [95% CI]; -3.8 [-5.0 to -2.6] and -4.8 [-6.2 to -3.4], respectively; $p < 0.001$ for both).

7.2.3.2 Patterns of exercise responses

Figure 7-1 demonstrates the patterns of change in HR and SpO_2 during the CPET and the 6MWT. During the CPET, HR increased linearly with time whereas, during the 6MWT, HR increased from the beginning of the test until the fifth decile (i.e. end of the third minute of the test) (ΔHR between the beginning of test and fifth decile; 32 ± 12 bpm; $p < 0.001$) with a subsequent plateau from the fifth decile to the tenth decile (i.e. sixth minute or test completion) (ΔHR between the fifth and tenth decile; 4 ± 4 bpm; $p = 0.34$). During the CPET, there was a linear decrease in SpO_2 (initial SpO_2: 97 ± 2% *versus* nadir SpO_2: 95 ± 3%; $\Delta SpO_2 = -1 \pm 3\%$; $p = 0.02$) whereas, during the 6MWT, there was a rapid reduction in SpO_2 from the beginning of the test until the third decile (i.e. end of the second minute of the test) (ΔSpO_2 between the beginning of the test and third decile; -3 ± 2%; $p = 0.01$) with a subsequent plateau from the third decile to the tenth decile (i.e. sixth minute or test completion) (ΔSpO_2 between the beginning of the third decile and tenth decile; -1.0 ± 1.5%; $p = 0.67$).

Table 7-3: Comparison of HR, SpO_2 and symptoms during the 6MWT and CPET

Variable (n = 20)	**CPET** mean ± SD	**6MWT** mean ± SD
Resting HR (bpm)	85 ± 13	83 ± 10
Peak HR (bpm)	128 ± 18	119 ± 15*
Peak HR (%pred HRmax)[#]	84 ± 11	79 ± 10*
ΔHR (bpm)	44 ± 16	37 ± 14
Resting SpO_2 (%)	97 ± 2	97 ± 1
Nadir SpO_2 (%)	95 ± 3	93 ± 2*
ΔSpO_2 (%)	-1 ± 3	-4 ± 2*
End-test BORGd	6.9 ± 2.6	3.1 ± 1.6**
End-test BORGf	6.8 ± 2.4	2.0 ± 1.9**

Abbreviations: 6MWT – Six-minute walk test; CPET – Cardiopulmonary exercise test; BORGd – Dyspnoea; BORGf – Leg fatigue; HR – Heart rate; SpO_2 - Arterial oxygen saturation measured via pulse oximetry; ΔSpO_2 – (Nadir SpO_2 – initial SpO_2).
Statistically significant differences between tests: *$p < 0.05$; **$p < 0.01$
[#] Maximum HR (HRmax) was calculated from the equation 220 - age.

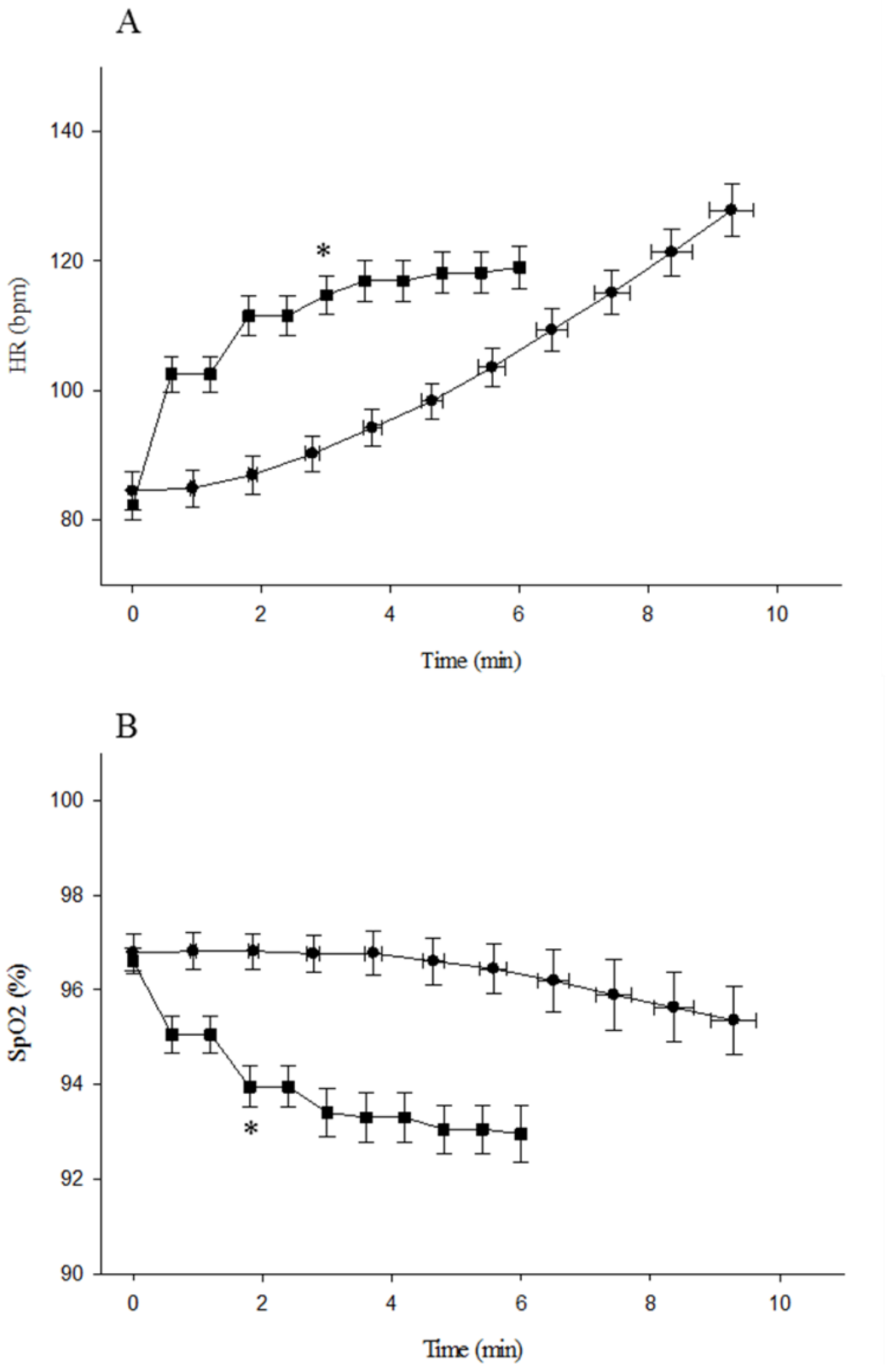

Figure 7-1: Patterns of responses for: A) heart rate (HR) and B) arterial oxygen saturation (SpO_2) for each test. Data are mean and standard error. All participants contributed to each decile (data point). ●, cardiopulmonary exercise test; ■, six-minute walk test. *Plateau from this decile to the tenth decile (i.e. sixth minute or test completion) of the six-minute walk test.

7.3 Discussion

This is the first study to compare peak exercise responses as well as patterns of change in HR and SpO_2 during the 6MWT with those during the CPET in people following curative intent treatment for NSCLC. The results demonstrated that the 6MWT elicited a somewhat lower peak HR than the CPET. In contrast, the magnitude of decrement in SpO_2 was greater during the 6MWT than during the CPET. Participants following curative intent treatment for NSCLC reported less symptoms of dyspnoea and leg fatigue at the end of the 6MWT than at the end of the CPET. Further, regarding the pattern of response, a plateau in the HR and SpO_2 responses occurred after the end of the third and second minute of the 6MWT, respectively, whereas during the CPET, there was a linear increase in HR and decrease in SpO_2 with increasing work rate.

7.3.1 Exercise responses

The peak HR achieved during the 6MWT was somewhat lower than that achieved during the CPET. However, the increase from resting to peak HR during the 6MWT was comparable to that during the CPET. This is due to the slight non-significant difference in resting HR during the tests (resting HR 83 ± 10 [6MWT] *versus* 85 ± 13 [CPET]; $p = 0.35$). The minimal difference in peak HR and similar ΔHR during the 6MWT and the CPET corroborate findings from previous studies in people with chronic lung disease such as IPF, moderate to severe COPD and exercise-induced pulmonary hypertension which showed either modest difference (92) or no difference (94-98) in peak HR between the tests. Three of the previous studies (94, 95, 97) have measured ventilatory responses during both the CPET and the 6MWT and have demonstrated that people with COPD achieved similar VO_{2peak} during the two tests. Although in the current study ventilatory responses during the 6MWT were not measured, the comparable magnitude of change from resting to peak HR (ΔHR) between the 6MWT and the CPET suggests that the 6MWT elicited a near maximum cardiac response and as such, the results of the 6MWT may be useful when prescribing walking training in people following curative intent treatment for NSCLC.

During the CPET, people following curative intent treatment for NSCLC achieved a VO_{2peak} of 15±3 $ml \cdot kg^{-1} \cdot min^{-1}$ or 63±15% predicted. The impairment in 6MWD was less, being 503±71 m or 81±10% predicted. Therefore, it seems that people following curative intent treatment for NSCLC have considerable impairment in peak exercise capacity, but relatively modest impairment in the capacity to walk as far as possible in 6 minutes. The implications of this finding are three-fold. First, there is evidence that the CPET is not routinely used to assess exercise capacity pulmonary rehabilitation programmes in Australia(338). Instead, the 6MWT is the exercise test of choice in 94% of Australia's pulmonary rehabilitation programmes. Therefore, for clinicians who are unable to access CPET, the 6MWT can be an alternative exercise test. However, people following curative intent treatment for NSCLC who present with modest impairments in 6MWD may have considerable impairment in peak exercise capacity, and therefore may still benefit from participating in exercise training. Second, given that the mean 6MWD was greater than 500m, or 80%predicted, it is possible that this test is not as responsive as it is in people with moderate-to-severe COPD to change following exercise training (339). Although earlier work in people with bronchiectasis, who were characterised by a high baseline 6MWD, demonstrated an increase in 6MWD of 41m (95% CI 19 to 63m) following 8 weeks of exercise training (340), alternative field-based tests, such as the modified incremental shuttle walk test may be more responsive to change following interventions. Third, the way in which the 6MWD has been used to prescribe the intensity of ground-based walk training in people with COPD may require some reconsideration in people following curative intent treatment for NSCLC. That is, in people with moderate-to-severe COPD, in whom the 6MWT has been demonstrated to elicit a similar peak HR as a CPET (94, 95), ground-based walking is often prescribed at an intensity equivalent to 75 to 80% of the average speed achieved on the 6MWT (89, 341). Given that the 6MWT elicits lower peak HR response in people following curative intent treatment for NSCLC, it is likely that intensity of ground-based walk training can be prescribed at a speed greater than 80% of the average speed achieved on the 6MWT.

Compared to the CPET, the current study demonstrated that the SpO_2 of people following curative intent treatment for NSCLC decreased significantly more during the 6MWT. This result also corroborates the findings of previous studies in people

with moderate to severe COPD (94-97, 342). These studies demonstrated that, although SpO_2 decreased during both the CPET and the 6MWT in people with moderate to severe COPD, SpO_2 decrements during the 6MWT were of greater magnitude than during the CPET (94-97, 342). One of the reasons for this finding might be that, compared with cycling, walking is known to elicit a lower ventilatory response, presumably due to a smaller accumulation of blood lactate (343). This lower level of ventilation during walking based exercise leads to greater desaturation (344, 345). The greater oxygen desaturation during the 6MWT suggests that this test can be used as a complementary test to the CPET in people following curative intent treatment for NSCLC as it may be more sensitive than the CPET to detect exercise-induced hypoxaemia in this population.

In keeping with an earlier study in people with moderate to severe COPD, the CPET elicited greater dyspnoea and leg fatigue than the 6MWT (94). One possible explanation for this result is that, compared with walking, cycling is known to impose a greater specific load on the quadriceps and result in a greater concentration of blood lactate on test completion (343, 346). That is, the load imposed on the quadriceps is likely to explain the increased perception of leg fatigue whilst the accumulation of blood lactate will increase the ventilatory response, which is likely to be perceived as dyspnoea (342, 346). Another possible explanation is that differences in how often dyspnoea and fatigue were measured during the tests may have influenced the end-test scores. That is, during the 6MWT, symptoms were only measured before the test and upon test completion. However, during the CPET, symptoms were measured prior to the test, minute-by-minute during the test and at test completion. It is likely that the increased frequency with which measures of dyspnoea and leg fatigue were collected during the CPET contributed to a greater end-test score in these symptoms. Support for this contention can be found in one study in 20 people with severe COPD that measured dyspnoea every minute during both the CPET and the 6MWT (96) and showed no difference in end-test dyspnoea between two tests (CPET 7 ± 2 *versus* 6MWT 6 ± 2; $p > 0.05$). Although it is reasonable to speculate that the high dyspnoea score reported by participants of that study at the end of the 6MWT could have been driven by the more frequent assessment of dyspnoea (i.e. minute-by-minute), participants in the study by Turner et al (96) had severe airflow obstruction (FEV_1 = 0.78 ± 0.25 L or 29 ± 8%

predicted) and limited maximum minute ventilation (VEmax = 32 ± 10 $L \cdot min^{-1}$). These characteristics may also have contributed to high dyspnoea scores at the end of the 6MWT.

7.3.2 Patterns of exercise responses

Data from the current study revealed clear differences in patterns of HR and SpO_2 responses during the 6MWT compared to the CPET. Whilst HR and SpO_2 during the CPET changed gradually and linearly with time, during the 6MWT these two variables changed exponentially over the first 2 to 3 minutes of the test, followed by a relative plateau until test completion. These plateaus observed in both HR and SpO_2 during the 6MWT in this study have been previously reported in people with moderate to severe COPD (94, 95). Aside from HR and SpO_2, these previous studies also demonstrated plateaus in patterns of responses of other cardiorespiratory variables such as oxygen consumption, minute ventilation, tidal volume and rate of carbon dioxide output during the 6MWT (94, 95). These plateaus reflect the way in which the 6MWT is conducted. That is, compared to the incremental CPET, the work rate during the 6MWT (i.e. walking speed) is chosen by the participant. As the chosen walking speed is almost constant after the initial acceleration phase of the 6MWT (95, 347), it is reasonable to assume that the work rate following this initial burst of acceleration is also constant.

7.3.3 Familiarisation with the six-minute walk test

The increase in 6MWD on the second 6MWT (19 m or 4%) is consistent with findings from studies in people with COPD (13 to 37 m or 4 to 9%) (92, 348, 349) and IPF (11 m or 4%) (92) and supports the use of two 6MWT when assessing people following curative intent treatment for NSCLC. The need for a third 6MWT was not assessed in the current study, however data from previous studies in people with COPD demonstrated no significant increase on a third 6MWT (96, 350).

Strengths and limitations

Although being the first to compare exercise responses between the 6MWT and the CPET, our sample size of 20 participants was relatively modest. Nonetheless, this sample size was similar to that of previous studies that compared the responses during the CPET to those during field-based walk tests in people with moderate to severe COPD (sample size range: 20 to 24 participants) (94-96) and greater to a previous study in people with heart failure (n = 15) (351). Another limitation is that ventilatory and metabolic responses during the 6MWT were not measured in the current study. Therefore, discussion pertaining to differences in VO_{2peak}, minute ventilation, inspiratory capacity (i.e. hyperinflation), lactate production and other important ventilatory and metabolic variables of exercise capacity was not possible and further investigation is needed. Additionally, people who underwent wedge resection or pneumonectomy for NSCLC were not included in the study, thus the results cannot be extended to all people undergoing lung resection for NSCLC.

7.4 Conclusions

This study suggests that the 6MWT elicits a somewhat lower peak HR than the CPET, however the magnitude of change from resting to peak HR was the same. Further, the 6MWT was more sensitive than the CPET at detecting oxygen desaturation in people following curative intent treatment for NSCLC. End-test symptoms of dyspnoea and leg fatigue were lower for the 6MWT and this might be related to the greater specific load borne by the quadriceps during the CPET. As opposed to the CPET, patterns of change in HR and SpO_2 during the 6MWT were not linear. Plateaus were observed in HR and SpO_2 responses during the 6MWT. These results suggest that the 6MWT should be considered a complementary test to the CPET and may also be useful when prescribing walking training in people following curative intent treatment for NSCLC. The 6MWT can either be undertaken before the CPET, in order to ensure that a patient will tolerate the CPET, or after the CPET, in order to investigate any oxygen desaturation not detected during the CPET. The 6MWD increased with test familiarisation, and therefore clinicians should perform at least two tests to account for this effect when using the 6MWT to evaluate the effect of an intervention in people following curative intent treatment for NSCLC.

CHAPTER 8

A RANDOMISED CONTROLLED TRIAL OF EXERCISE TRAINING FOR PEOPLE FOLLOWING CURATIVE INTENT TREATMENT FOR NON-SMALL CELL LUNG CANCER

Overview

This Chapter presents the methodology of the randomised controlled trial (RCT) performed in this programme of research. The details of the study design are provided, including a description of participant inclusion and exclusion criteria, recruitment strategies, randomisation process and blinding procedures. The assessment protocol and measurements made at baseline and post-intervention were described in Chapter 5. Details of the data management and statistical analyses used to assess the effects of exercise training following curative intent treatment for non-small cell lung cancer (NSCLC) as well as the results, discussion and conclusions are presented.

The specific question answered in this Chapter is: What are the effects of supervised exercise training on exercise capacity, health-related quality of life (HRQoL), peripheral muscle force, physical activity and sedentary behaviour, lung function, functional limitation resulting from dyspnoea and fatigue, and feelings of anxiety and depression in people following curative intent treatment for NSCLC?

The hypothesis is that supervised exercise training will not change resting lung function of people following curative intent treatment for NSCLC, but will confer benefits in all other outcome measures, over and above any change seen following usual care.

8.1 Study design

Overview

This study was a single-blind RCT. Data collection was performed between February 2012 and April 2014. An overview of the study design is provided in Figure 8-1. Measurements were collected of exercise capacity, HRQoL, peripheral muscle force, physical activity and sedentary behaviour, resting lung function, functional limitation resulting from dyspnoea and fatigue, and feelings of anxiety and depression in people 6 to 10 weeks after lobectomy for NSCLC or, for those who went onto receive chemotherapy, 4 to 8 weeks after their last cycle of chemotherapy. Assessments were initiated after participants gave written informed consent and were undertaken over 2 or 3 days, with a minimum of 24 hours between each assessment day, over a period of 2 to 3 weeks. Participants then were randomised to either the exercise training group (EG), which received 8 weeks of exercise training, or the non-exercise training control group (CG), which received weekly phone calls for 8 weeks. On completion of the intervention period all measurements were repeated.

8.1.1 Ethics approval and trial registration

The study was approved by the Human Research Ethics Committees of Sir Charles Gairdner Hospital (SCGH) (approval number 2011/105), Royal Perth Hospital (RPH) (RA- 11/033) and Curtin University (approval number HR 178/2011). It was also registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) (registration number ACTRN12611000864921).

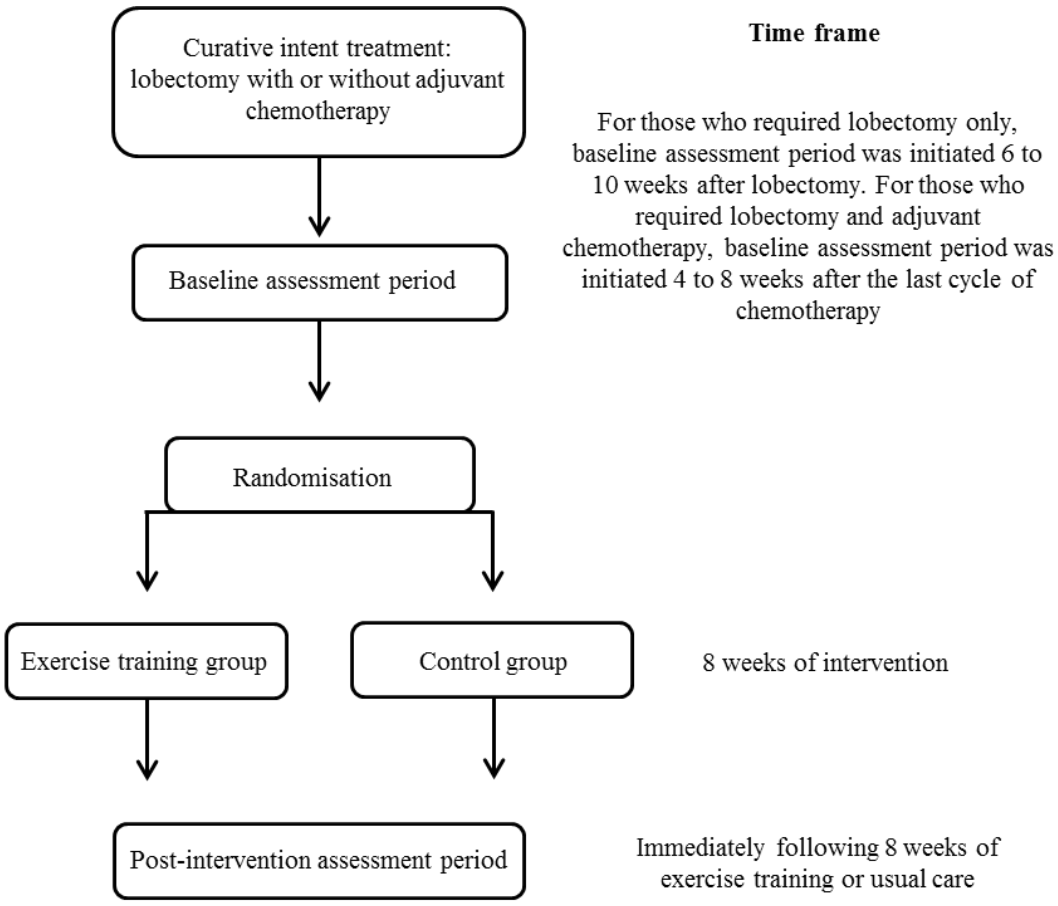

Figure 8-1: Overview of the study design

8.1.2 Participants

8.1.2.1 Inclusion criteria

People were eligible to participate in this study if they had a diagnosis of primary NSCLC (stage I, II or IIIA) and were 6 to 10 weeks following lobectomy or, for those who required adjuvant chemotherapy following surgery, 4 to 8 weeks after completion of their last cycle.

8.1.2.2 Exclusion criteria

Exclusion criteria comprised; (i) need for pneumonectomy, (ii) presence of any co-morbid condition thought to compromise safety during the assessments, (iii) severe neuromusculoskeletal limitations that would impact on assessments or the capacity to participate in exercise training, (iv) participation in a programme of supervised exercise training in the last 3 months or, (v) inability to understand spoken or written English.

8.1.3 Recruitment

People with NSCLC were recruited from outpatient clinics, referrals to the exercise training programme at SCGH and RPH as well as a private thoracic surgery clinic in Perth.

8.1.4 Baseline assessments protocol

The choice to undertake baseline assessments, for those who required a lobectomy without adjuvant chemotherapy, 6 to 10 weeks following surgery was made following consultation with thoracic surgeons as this time period was expected to be sufficient to allow wound healing and resolution of post-operative pain. For those who required adjuvant chemotherapy following surgery, baseline assessments took place 4 to 8 weeks following their last cycle, to allow for resolution of the adverse effects of chemotherapy (i.e. nausea).

Post-intervention assessments occurred immediately following the completion of the 8-week intervention period. For both baseline and post-intervention assessments, the first and second assessment days took place at either SCGH or RPH. On the first day

of assessments, participants performed two six-minute walk tests (6MWT), completed questionnaires pertaining to HRQoL, symptoms of anxiety and depression and dyspnoea, had their handgrip force measured and were given two physical activity monitors to be worn over 7 consecutive days. Following this period of 7 days, participants returned for the second day of assessments that comprised lung function tests as well as a cardiopulmonary exercise test (CPET). The third assessment day comprised measurement of isometric quadriceps muscle torque and took place at Curtin University. As the university is approximately 15 km from either of the hospitals, participants were given the option to decline this assessment.

8.1.5 Randomisation

Following the baseline assessments, participants were randomly assigned to either the EG or the CG. The randomisation sequence was generated using a computer and concealed using opaque envelopes. It was stratified according to the hospital from which the participant was recruited (SCGH or RPH) and for the use (or not) of adjuvant chemotherapy. The sequence was also blocked so that for every two participants randomised, one was allocated to the EG and one to the CG.

8.1.6 Blinding

The primary investigator (VC), who was responsible for the baseline and post-intervention assessments was neither aware of whether a participant had been allocated to the EG or the CG nor involved with the randomisation process or the training of participants. Training was supervised by the physiotherapists responsible for running the exercise training programmes at SCGH and RPH.

8.1.7 Withdrawal criteria, intention-to-treat criteria, data imputation and defining adherence to exercise training

Participants who had their NSCLC upstaged to stage IIIB or IV NSCLC were withdrawn from the study as they no longer met the study inclusion criteria. Intention-to-treat (ITT) analyses were performed in order to minimise bias resulting from attrition from the study as well as bias that results from including only those participants who were adherent with the treatment (352). Two methods of ITT analyses were undertaken in this RCT. First, ITT analyses were performed without

data imputation. That is, all data collected in all participants, regardless of adherence to intervention, were included in the analysis however, no imputation was performed. Second, all data collected in all participants, regardless of adherence to intervention, were included in the analysis however, missing data at the post-intervention assessment period were imputed using the baseline-observation-carried-forward (BOCF) method (353). This method of data imputation has been suggested by regulatory agencies to evaluate clinical trials (353, 354). In addition to these two methods of ITT analyses, individual data were analysed in order to report effects of treatment in those who were deemed to be adherent with the intervention. Specifically, participants in the EG who attended at least 60% of exercise training sessions over the 8-week training period (i.e. 15 of 24 sessions) were classified as "adherent" with exercise training.

8.2 Measurements

8.2.1 Primary outcomes

8.2.1.1 Exercise capacity

8.2.1.1.1 Cardiopulmonary exercise test

A symptom-limited ramp cycle ergometry exercise test was be performed on an electronically braked bicycle ergometer (ER 900; Jaeger, Hoechberg, Germany) in accordance with published guidelines (72). The rate at which the work rate increased during the test was determined using an equation that considered age, height, gender, forced expiratory volume in one second (FEV_1) and single breath diffusing capacity for carbon monoxide (D_LCO) (280). This individualised approach for work rate increments was used to attain the recommended CPET duration of 8 to 12 minutes (72, 280, 281). Increments varied from 1 W every 12 seconds (i.e. 5 W per minute) to 1 W every 5 seconds (i.e. 12 W per minute). The peak rate of oxygen consumption (VO_{2peak}) and maximum work rate (Wmax) achieved during the CPET were expressed in absolute values and as a percentage of the predicted value in a healthy population (282). Further details pertaining to the CPET assessment have been described in Chapter 5 (heading 5.2.1.1 Exercise capacity).

8.2.1.1.2 Six-minute walk test

Functional exercise capacity was evaluated using the 6MWT, which was undertaken according to a protocol based on the American Thoracic Society (ATS) recommendations (77). The 6MWT was performed over a 45-m level straight course within an enclosed corridor. Standardised instructions were read to each participant prior to commencing the test and standardised encouragement was given at the end of every minute. Also, at the end of every minute, measures were collected of heart rate (HR) (Polar a1 heart rate monitor; Polar Electro Oy, Kempele, Finland) and arterial oxygen saturation measured via pulse oximetry (SpO_2) (finger sensor and handheld pulse oximeter, Rad-57; Masimo Corporation, Irvine, CA, USA). During both the baseline and post-intervention assessment periods two tests, separated by a 30-minute rest period, were conducted and the best distance achieved (i.e. six-minute walk distance [6MWD]) was recorded as the test result. Data of 6MWD were expressed in absolute values and as a percentage of the predicted value in a healthy population (196). Further details pertaining to the 6MWT assessment have been described in Chapter 5 (heading 5.2.1.1 Exercise capacity).

8.2.1.2 Health-related quality of life

8.2.1.2.1 Medical outcomes study short form 36 general health survey (SF-36)

The SF-36 is a self-complete questionnaire which assesses generic HRQoL (287). It comprises two major components: physical (physical component score [PCS]) and mental (mental component score [MCS]). The PCS comprise four domains; physical functioning, physical role functioning, bodily pain and, general health. The MCS also comprises four domains; vitality, social functioning, emotional role functioning and, mental health. Further details pertaining to the SF-36 have been described in Chapter 5 (heading 5.4.1.2 Health-related quality of life).

8.2.1.2.2 The functional assessment of cancer therapy – lung scale (FACT-L) version 4

The FACT-L version 4 is a self-complete 36-item questionnaire (290). It comprises five subscales; physical well-being, social/family well-being, emotional well-being, functional well-being as well as a separate lung cancer subscale. Further details

pertaining to the FACT-L have been described in Chapter 5 (heading 5.4.1.2 Health-related quality of life).

8.2.1.2.3 The European organisation for research and treatment of cancer, quality of life questionnaire core 30 (EORTC QLQ-C30) version 3

The EORTC QLQ-C30 comprises 15 scales (291). Five scales pertain to function (i.e. physical, role, emotional, cognitive, and social), three scales pertain to symptoms (i.e. fatigue, pain, and nausea), and there is also one global measure of health status. The remaining six scales are single-item scales that assess the following symptoms; dyspnoea, appetite loss, sleep disturbance, constipation and diarrhoea, and the perceived financial impact of the disease treatment. The questionnaire also includes, as an additional page, the lung cancer subscale (the EORTC-LC13). This subscale addresses 13 symptoms specific to people with lung cancer such as cough, dyspnoea, haemoptysis and chest pain (202). Further details pertaining to the EORTC QLQ-C30 have been described in Chapter 5 (heading 5.4.1.2 Health-related quality of life).

8.2.1.3 Peripheral muscle force

8.2.1.3.1 Isometric quadriceps torque and isometric handgrip force

Maximal isometric torque of the quadriceps was measured in an upright seated position using the HUMAC NORM isokinetic dynamometer (CSMi; Stoughton, MA, USA). The dominant leg was chosen and participants were asked to perform five maximum contractions of the quadriceps at 60º of knee flexion. Each contraction was separated by 60 seconds. The contraction that generated the highest torque, and was within 5% of another effort, was recorded as the test result. Measures were expressed in absolute values and as a percentage of the predicted value in a healthy population (294).

Isometric handgrip force was measured using a hydraulic hand dynamometer (Jamar dynamometer; JA Preston Corporation; Jackson, MI, USA). Peak handgrip force was assessed bilaterally, with the elbow at 90° of flexion and the forearm and wrist in a neutral position. Measures were expressed in absolute values and as a percentage of the predicted value in a healthy population (295). Further details pertaining to the

assessment of isometric quadriceps torque and isometric handgrip force have been described in Chapter 5 (heading 5.2.1.3 Peripheral muscle force).

8.2.1.4 Physical activity and sedentary behaviour

Participants were asked to wear two activity monitors (i.e. the SenseWear armband [SAB] and the Stepwatch activity monitor [SAM]) for 7 consecutive days, during waking hours. They were asked to simultaneously attach these two activity monitors as soon as they woke up each day and remove them during showering and swimming activities as well as to sleep. Further details pertaining to the assessment of physical activity and sedentary behaviour have been described in Chapter 5 (heading 5.4.1.4 Physical activity) and Chapter 6 (heading 6.1.2 Data management).

Physical activity and sedentary behaviour data management

In people following curative intent treatment for NSCLC, there are no studies that have investigated the minimum number of days and hours per day an activity monitor needs to be worn in order to reliably measure physical activity and sedentary behaviour. The criteria used in the current study to define a minimum valid sample of activity monitoring was at least 4 full days of data (defined as $\geq$ 10 hours/day wearing the monitors), including one weekend day. The justification for these criteria has been presented in Chapter 5 (heading 5.2.1.4 Physical activity) and Chapter 6 (heading 6.1.2 Data management). Data collected over all days that met these criteria were averaged for analysis.

8.2.2 Secondary outcomes

8.2.2.1 Lung function

The Medgraphics Elite Series DX plethysmograph (Medical Graphics Corporation, St Paul, MN, USA) was used to assess lung function and the equipment was calibrated prior to every test in accordance with the manufacturer's recommendations. Lung function testing comprised measures made using spirometry (forced vital capacity [FVC] and slow vital capacity [SVC] manoeuvres), body plethysmography and diffusing capacity for carbon monoxide. Measurements were expressed in absolute values and, where possible, as a percentage of the predicted

value in a healthy population (306-308). Further details pertaining to the assessment of lung function have been described in Chapter 5 (heading 5.2.2.1 Lung function).

8.2.2.2 Functional limitation resulting from dyspnoea and fatigue

8.2.2.2.1 Modified medical research council dyspnoea scale (MMRC)

Functional limitation resulting from dyspnoea was assessed by the MMRC dyspnoea scale (309, 310). This simple scale comprises five statements assigned a grade which ranges from 0 to 4. The participant selects the statement which best reflects their level of limitation in activities of daily life due to breathlessness. The MMRC dyspnoea scale is a valid method of categorising people with chronic lung disease in terms of their functional disability (311).

8.2.2.2.2 Functional assessment of chronic illness therapy - fatigue subscale (FACIT-Fatigue)

Fatigue was assessed using the FACIT-Fatigue (312). The FACIT-Fatigue has 13 items answered on a 5-point rating scale and is based on a 7-day recall period. Scores range between 0 and 52, with lower scores reflecting greater fatigue. The questionnaire has good reliability and validity based on analyses of data from people with cancer and rheumatoid arthritis (312, 313).

8.2.2.3 Feelings of anxiety and depression

8.2.2.3.1 The hospital anxiety and depression scale (HADS)

Feelings of anxiety and depression measured using the HADS (314). It comprises 14 statements describing symptoms of depression (7 items) and anxiety (7 items). Response options for each question range from 0 to 3, with a total range score between 0 and 21 for the depression and anxiety subscales. Further details pertaining to the HADS have been described in Chapter 5 (heading 5.2.2.3 Feelings of anxiety and depression).

8.3 Interventions

8.3.1 Control group

Participants in the CG received weekly phone calls from the research assistant for 8 weeks. The phone calls consisted of a general conversation about their health, family, social activities as well as standardised questions related to the past week. Participants in the CG were asked as to whether they had seen a doctor, whether they were doing any kind of exercise, how well they thought they were recovering following the curative intent treatment and whether they had any further questions about the study. These phone calls aimed to minimise bias resulting from differences in attention provided by the investigators to the participants in either group during the intervention period as well as maintain contact with those in the CG to optimise their retention in the study. After the post-intervention assessment period participants of the CG were offered the opportunity to participate in exercise training (i.e. exercise training programmes at SCGH and RPH).

8.3.2 Exercise training group

Participants in the EG underwent an 8-week exercise training programme. This programme was embedded within the exercise training programmes at SCGH and RPH and consisted of supervised training sessions of 60 minutes duration, which participants completed 3 times per week. In the event that a participant could only attend two supervised sessions per week, they were provided with a cycle ergometer (OBK600A; Orbit fitness equipment, Perth, WA, Australia) to use at home for one training session per week. At the time the cycle ergometer was provided, a physiotherapist visited the participant's home to explain how to use the equipment. With the exception of the cycle ergometer training, no other home exercise programme was given.

Each class comprised aerobic (walking and cycling) and resistance training (upper and lower limbs). The exercise classes took place in the main hospital corridor and in the Gymnasium in the Physiotherapy Department at SCGH and in the Gymnasium in the Physiotherapy Department at RPH.

Participants were familiarised with both the BORG scale for dyspnoea (BORGd) (0-10) and the rating of perceived exertion (RPE) scale (6-20), as a combination of these were used to prescribe exercise intensity and for progression of the exercises (see headings 8.3.2.1 Aerobic training and 8.3.2.2 Resistance training). Dyspnoea was measured before and after the 20-minute walking programme and following all other exercises using the BORGd scale. The RPE was measured after walking and at the end of each exercise to determine exercise progression. The rationale for using a combination of scales was that, for some participants, dyspnoea might not have been their main symptom limiting performance for all exercises (40). For instance, Killian et al (355) measured dyspnoea and leg fatigue on completion of a CPET in 97 people with chronic airflow limitation. The study demonstrated that 31% of participants (n = 30) had similar dyspnoea and leg fatigue scores on completion of the CPET; 26% of participants (n = 25) presented more dyspnoea than leg fatigue and 43% of participants (n = 42) reported more leg fatigue than dyspnoea on completion of the CPET (355).

8.3.2.1 Aerobic training

8.3.2.1.1 Walking

Participants walked in 100-m long corridor (SCGH) or on a treadmill (RPH) for 20 minutes. The initial speed was set at 80% (for corridor walking) and 70% (for treadmill walking) of the average speed achieved during the baseline 6MWT (89).

For example:

6MWD = 450 m → average speed = 4.5 km/h → initial speed (corridor) = 3.6 km/h, that is, 1200 m in 20 min

6MWD = 450 m → average speed = 4.5 km/h → initial speed (treadmill) = 3.2 km/h

Arterial oxygen saturation and pulse rate measured via pulse oximetry were recorded before and after the 20-minute walk. Participants were encouraged to take regular rests in the case of desaturation (SpO_2 less than 88%) or intolerable symptoms of dyspnoea or leg fatigue. They were encouraged to continue walking provided that symptoms were tolerable and SpO_2 was $\geq$ 88%.

Exercise intensity (i.e. walking speed) was increased if the participant was able to walk for 20 minutes continuously providing symptoms were tolerable (i.e. BORGd 3-5 and RPE 12-16) and SpO_2 was within acceptable limits (≥ 88%). In participants who rested, the number or duration of rests were decreased where possible, providing SpO_2 was maintained within acceptable limits.

Progression in walking training was assessed by comparing both distance walked and walking speed achieved during the initial and final sessions of supervised exercise training.

8.3.2.1.2 Cycle ergometer

This comprised both endurance and power training.

Endurance training

The initial work rate was set at 60% of the Wmax achieved during the CPET performed at the baseline assessment (89). For the first training session, participants aimed to cycle for 5 minutes continuously. For the subsequent training sessions the aim was to cycle for 10 minutes, which could be either continuous or intermittent, depending on symptoms. Ten minutes was the aim as it allowed for a minimum of 30 minutes of aerobic exercise (taking into account the 20 minutes of walking training), as recommended by the current official ATS/European Respiratory Society (ERS) statement in pulmonary rehabilitation (54). Cycle training was interspersed with rests until symptoms were tolerable to allow for the completion of training. Also, SpO_2 and pulse rate were measured before and after the endurance training. Once 10 minutes of continuous cycling was achieved, providing symptoms were tolerable (i.e. BORGd 3-5 and RPE 12-16) and SpO_2 was within acceptable limits (≥ 88%), then work rate was increased by increments of 5W.

Power training

The initial work rate was set at 80% of the Wmax achieved during the CPET performed at the baseline assessment (356). Participants performed two periods of 2 minutes cycling interspersed by rest until symptoms were tolerable. Work rate was increased by increments of 5 W providing symptoms were tolerable (i.e. BORGd 3-5

and RPE 12-16) and SpO_2 was within acceptable limits (≥ 88%). The power training was prescribed in order to provide higher intensity of training aiming at achieving greater physiological benefits (357). Additionally, as the assessment of maximal exercise capacity (CPET) was undertaken on a cycle ergometer, the power training was likely to maximise cycling exercise responses.

As both work rate and cycling time were used to progress the cycle ergometer training, the product of work rate and cycling time (in W·min) was used as the variable to assess the progression of cycle ergometer training. Progression in cycle ergometer training was assessed by comparing the product of work rate and cycling time (in W·min) achieved during the initial and final sessions of supervised exercise training.

8.3.2.2 Resistance training

8.3.2.2.1 Lower limbs (Step ups)

Step ups were undertaken within parallel bars in two sets of 10 repetitions. Initially, participants were allowed to hold onto the bars. The sequence was up-up-down-down leading with alternate leg for each set of 10 repetitions. Progression was made by: (i) increasing from two sets to three sets of 10 repetitions; (ii) taking the hands off from the parallel bars; (iii) increasing the height (2 to 3 risers) and; (4) adding hand weights.

Progression in step up exercise was assessed by comparing the number of step ups performed during the initial and final sessions of supervised exercise training.

8.3.2.2.2 Upper limbs and stretching exercises

Upper limbs

Exercises with hand weights for the biceps brachii muscle (elbow flexion) and deltoid muscle (short-lever shoulder abduction) were undertaken. Upper limb training was undertaken in three sets of 10 repetitions (initial weights: 1.5 kg for women and 2 kg for men). Hand weights were increased providing symptoms were tolerable (RPE 12-16).

As weights, sets and repetitions were used to progress the upper limbs training, the product of these three variables (in kg·sets·reps) was used as the variable to assess progression of the upper limb training. Progression assessed by comparing the product of weights lifted, number of sets and number of repetitions (in kg·sets·reps) achieved during the initial and final sessions of supervised exercise training.

Stretching exercises

Stretches consisted of trunk side flexion (both sides) and trunk rotation (both sides) positions.

8.4 Statistical analyses

8.4.1 Sample size calculation

Earlier work, using a single-group design, demonstrated an increase in exercise capacity, measured via cycle ergometry of 30 ± 22 W, in participants who had completed a period of exercise training which was initiated on completion of treatment of lung cancer (31). However, it was anticipated that the magnitude of between-group differences will be smaller than 30 W in the current study, as the CG may improve slightly over time without any specific intervention. Therefore, prospective sample size calculations were undertaken to ensure adequate power ($\alpha = 0.05$, $1 - \beta = 0.8$) to detect a between-group difference of 25 ± 22 W. To detect a difference of this magnitude, 13 participants per group were required.

8.4.2 Statistical analyses

Statistical analyses were performed using SPSS® (Statistical Package for Social Sciences, version 22.0 for Windows). The distribution of data was examined by graphical (frequency histograms and box plots) and statistical methods (Shapiro-Wilk test). At baseline, between-group comparisons of continuous data were undertaken using either independent-samples *t*-test or the Mann-Whitney U test. Pearson Chi-square test was used to compare categorical data. Progression of training work load was assessed using paired *t*-test. Measures collected at baseline and following the intervention period (i.e. within-group analysis) were compared using either paired *t*-test or Wilcoxon test. For variables that followed a normal

distribution, differences between measures collected at baseline and following the intervention period are reported as mean difference (MD) and 95% confidence interval (CI). Between-group comparisons of the MDs of measures collected at baseline and following the intervention period were undertaken using independent-samples *t*-test or the Mann-Whitney U test. When baseline measures were different between EG and CG groups, between-group comparisons were undertaken using analysis of covariance (ANCOVA) using the baseline measure as the covariant. For all analyses, a p value ≤ 0.05 was considered significant. Data are expressed as either mean ± standard deviation (SD) or median [interquartile range].

8.5 Results

From February 2012 to April 2014, 96 people following curative intent treatment for NSCLC were screened to participate in this study, of whom 71% (n = 68) were eligible and approached. The consent rate was 26% (n = 18). Of the 23 participants who completed the cross-sectional study presented in Chapter 5 and were invited to participate in this RCT, five (22%) chose not to participate. One participant was withdrawn due to their cancer being upstaged to stage IIIB NSCLC. Seventeen participants underwent the baseline assessments and were randomised to either the EG or the CG. The study flow diagram, including the reasons for declining participation, is presented in Figure 8-2.

Nine participants (53%) were recruited from SCGH and eight (47%) participants were recruited from RPH. Of the nine participants recruited from SCGH, five (56%) were randomised to the EG and four (44%) to the CG. Of the eight participants recruited from RPH, four (50%) were randomised to the EG and four (50%) to the CG. Six participants (35%) underwent a left upper lobectomy, five (29%) underwent a right upper lobectomy, five (29%) underwent a right lower lobectomy and one (6%) underwent right middle lobectomy. The average time between lobectomy and the first day of assessment was 55 ± 19 days. Two participants (12%) received adjuvant chemotherapy. One was randomised to the EG and the other to the CG. For these participants, the time lapse between the last cycle of adjuvant chemotherapy and first day of assessment was 28 and 55 days.

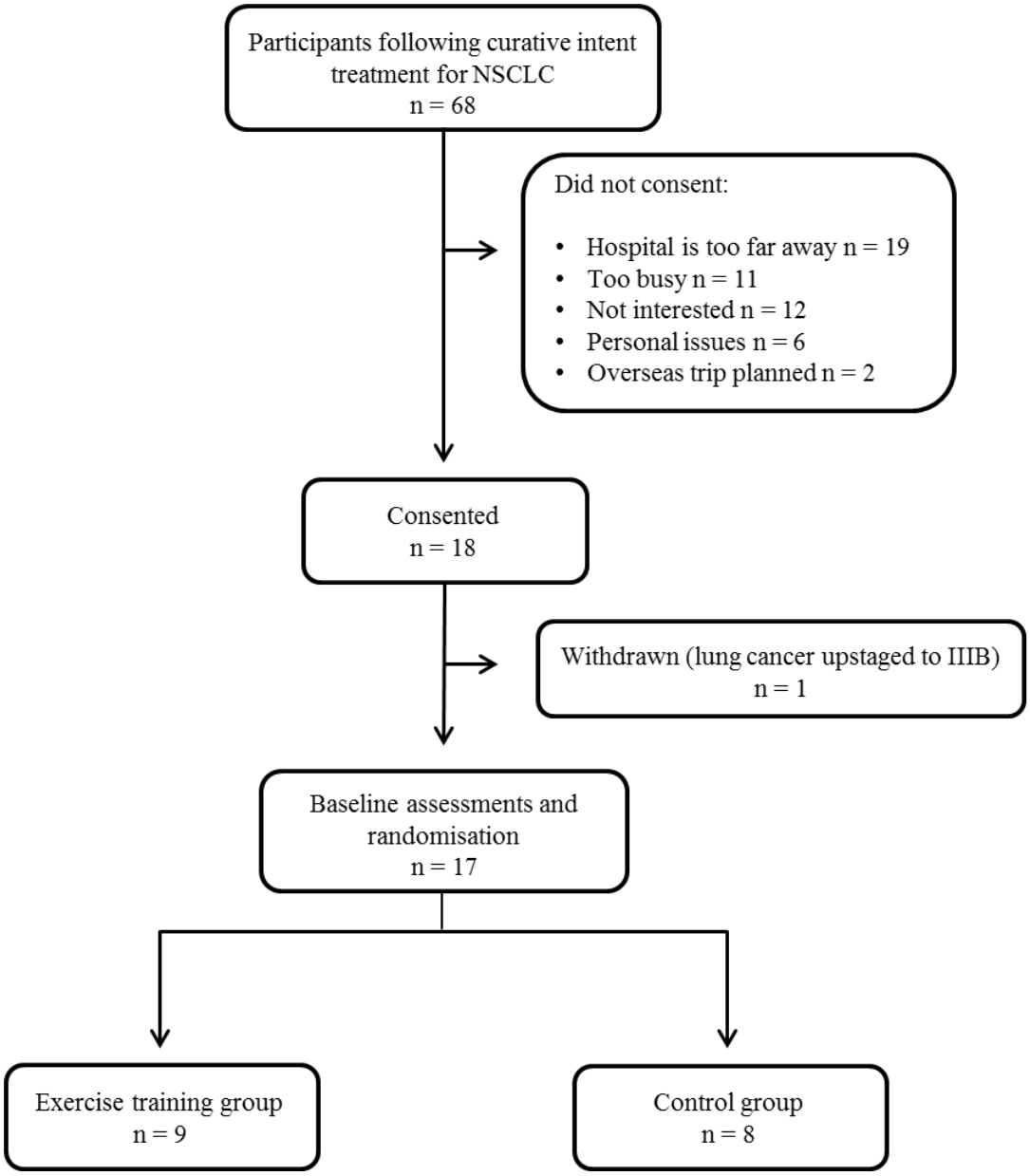

Figure 8-2: Study flow diagram

8.5.1 Baseline characteristics

8.5.1.1 Anthropometrics, lung function and medical history

At baseline, there were no differences between the EG and CG in anthropometrics, gender distribution, number of participants diagnosed with chronic obstructive pulmonary disease (COPD), type and stage of NSCLC, type of surgery undergone or number of participants who received adjuvant chemotherapy (Table 8-1). Pertaining to lung function, the FVC (%pred) was lower in the EG (MD [95% CI] -12 [-23 to -1]%pred; $p = 0.03$). Both groups were characterised by mild airflow obstruction (FEV_1/FVC 62 ± 14% [EG] and 62 ± 11% % [CG]; FEV_1 61 ± 17% %pred [EG] and 71 ± 15% %pred [CG]).

8.5.1.2 Exercise capacity

8.5.1.2.1 Cardiopulmonary exercise test

At baseline, the duration of the CPET as well as work rate increments during the test were similar between groups (duration 9 ± 2 min [EG] *versus* 9 ± 1 min [CG]; work rate increments 8 ± 2 W [EG] *versus* 8 ± 3 W [CG]; $p > 0.05$ for both). There were no differences between the EG and CG in any of the variables collected as part of the CPET (Table 8-2).

8.5.1.2.2 Six-minute walk test

At baseline, none of the participants required a rest during the 6MWT. There were no differences between the EG and CG in any of the variables collected as part of the 6MWT (Table 8-2).

Table 8-1: Baseline anthropometrics, lung function and medical history

Variable	Total sample (n=17) *mean ± SD*	Exercise group (n=9) *mean ± SD*	Control group (n=8) *mean ± SD*	*p value*
Age (yr)	67 ± 9	66 ± 10	68 ± 9	*0.617*
Height (cm)	165 ± 12	164 ± 14	166 ± 11	*0.801*
Weight (kg)	72 ± 21	67 ± 14	77 ± 27	*0.332*
BMI ($kg \cdot m^{-2}$)	26 ± 6	25 ± 5	27 ± 6	*0.355*
Smoking (pack/years)	38 ± 15	49 ± 27	35 ± 24	*0.261*
FEV_1 (L)	1.65 ± 0.49	1.53 ± 0.47	1.78 ± 0.50	*0.296*
FEV_1 (%pred)	66 ± 17	61 ± 17	71 ± 15	*0.207*
FVC (L)	2.68 ± 0.69	2.51 ± 0.76	2.87 ± 0.58	*0.287*
FVC (%pred)	80 ± 12	74 ± 11	86 ± 10	*0.033**
FEV_1/FVC (%pred)	62 ± 12	62 ± 14	62 ± 11	*0.984*
TLC (L)	4.73 ± 1.19	4.58 ± 1.56	4.91 ± 0.64	*0.586*
TLC (%pred)	86 ± 14	82 ± 16	90 ± 12	*0.263*
FRC (L)	2.94 ± 0.78	2.87 ± 1.00	3.02 ± 0.47	*0.714*
FRC (%pred)	97 ± 20	94 ± 20	100 ± 21	*0.544*
D_LCO ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	13.7 ± 3.6	12.8 ± 3.3	14.7 ± 3.8	*0.287*
D_LCO (%pred)	53 ± 12	49 ± 11	57 ± 13	*0.215*
MVV ($L \cdot min^{-1}$)	62 ± 21	60 ± 25	64 ± 28	*0.690*
MVV (%pred)	63 ± 16	59 ± 15	67 ± 18	*0.313*
	n **%**	**n** **%**	**n** **%**	
Gender, male/female	5/12 29/71	3/6 30/70	2/6 25/75	0.707
COPD	9 53	5 56	4 50	0.819
Type of NSCLC				
Adenocarcinoma	10 59	5 56	5 63	0.772
Squamous cell carcinoma	6 35	4 44	2 25	0.402
Large cell carcinoma	1 6	0 0	1 12	0.274
NSCLC stage				
I	14 82	7 78	7 88	0.229
II	2 12	2 22	0 0	0.156
IIIA	1 6	0 0	1 12	0.274
Type of surgery (lobectomy)				
Open	8 47	4 44	4 50	0.819
VATS	9 53	5 56	4 50	0.783
Adjuvant chemotherapy	2 12	1 11	1 12	0.929

Abbreviations: BMI – Body-mass index; COPD – Chronic obstructive pulmonary disease; D_LCO – single breath diffusing capacity for carbon monoxide; FEV_1 – Forced expiratory volume in one second; FRC – Functional residual capacity; FVC – Forced vital capacity; MVV – Maximum voluntary ventilation; NSCLC – Non-small cell lung cancer; SD – Standard deviation; TLC – Total lung capacity; VATS – Video-assisted thoracoscopic surgery.
**Statistically significant difference between groups.*

Table 8-2: Baseline exercise capacity

Variable	Total sample (n=17) *mean ± SD*	Exercise group (n=9) *mean ± SD*	Control group (n=8) *mean ± SD*	*p value*
CPET				
VO_{2peak} ($L \cdot min^{-1}$)	1.04 ± 0.30	1.01 ± 0.22	1.08 ± 0.40	*0.666*
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	14.6 ± 12.9	15.3 ± 3.2	13.9 ± 2.6	*0.322*
VO_{2peak} (%pred)	62 ± 16	60 ± 16	64 ± 17	*0.596*
Wmax (W)	74 ± 26	71 ± 20	77 ± 32	*0.655*
Wmax (%pred)	69 ± 18	69 ± 22	69 ± 15	*0.967*
BORGd on completion CPET	6.4 ± 2.7	6.9 ± 2.4	5.8 ± 3.0	*0.397*
BORGf on completion CPET	6.4 ± 2.3	5.6 ± 2.3	7.4 ± 2.1	*0.108*
Nadir SpO_2 (%)	94 ± 4	94 ± 2	94 ± 6	*0.926*
HRmax (bpm)	127 ± 18	127 ± 19	127 ± 18	*0.969*
BR (%)	28 ± 15	25 ± 16	32 ± 14	*0.377*
O_2 pulse ($ml \cdot beat^{-1}$)	8 ± 3	8 ± 2	8 ± 3	*0.717*
AT (%VO_{2peak})	62 ± 9	62 ± 9	63 ± 10	*0.772*
VEmax/MVV (%)	72 ± 15	75 ± 17	68 ± 14	*0.293*
6MWT				
6MWD (m)	501 ± 75	521 ± 75	480 ± 73	*0.273*
6MWD (%pred)	80 ± 11	83 ± 11	77 ± 10	*0.256*
BORGd on completion 6MWT	3.4 ± 1.5	3.4 ± 1.7	3.3 ± 1.4	*0.864*
BORGf on completion 6MWT	2.2 ± 2.0	1.4 ± 1.7	3.0 ± 1.4	*0.092*
Nadir SpO_2 (%)	92 ± 3	92 ± 3	92 ± 2	*0.909*
Peak HR (bpm)	122 ± 12	123 ± 13	121 ± 10	*0.736*

Abbreviations: 6MWD – Six0minute walk distance; 6MWT – Six-minute walk test; AT – Anaerobic threshold as a percentage of the VO_{2peak}; BORGd – Dyspnoea; BORGf – Fatigue; BR – Breathing reserve; CPET – Cardiopulmonary exercise test; HR – Heart rate; HRmax – Maximal heart rate; O_2 pulse – Oxygen pulse; SD – Standard deviation; SpO_2 - Arterial oxygen saturation measured via pulse oximetry; VEmax/MVV – Maximum minute ventilation, maximum voluntary ventilation ratio; VO_{2peak} – Peak rate of oxygen consumption; Wmax – Maximum work rate.

8.5.1.3 Health-related quality of life

8.5.1.3.1 Medical outcomes study short form 36 general health survey

At baseline, the CG reported lower scores for the MCS and for the domains of role physical and role emotional of the SF-36 ($p < 0.05$ for all), indicating greater impairment in HRQoL (Table 8-3).

8.5.1.3.2 The functional assessment of cancer therapy – lung scale, version 4

At baseline, the CG reported lower scores for the functional well-being and lung cancer subscales as well as for the total score of the FACT-L ($p < 0.05$ for all), indicating greater impairment in HRQoL (Table 8-3).

8.5.1.3.3 The European organisation for research and treatment of cancer, quality of life questionnaire core 30, version 3

At baseline, there were no differences between the EG and CG in scores for the EORTC QLQ-C30 (Table 8-3).

8.5.1.4 Peripheral muscle force

8.5.1.4.1 Isometric quadriceps torque and isometric handgrip force

Seven of the nine participants in the EG (78%) and five of the eight participants in the CG (63%) attended Curtin University to undergo the assessment of isometric quadriceps torque. At baseline, there was no difference between the EG and CG in isometric quadriceps torque (Table 8-4). Further, there was no difference between the EG and CG in isometric handgrip force (Table 8-4).

Table 8-3: Baseline health-related quality of life

Variable	Total sample (n=17) *mean ± SD*	Exercise group (n=9) *mean ± SD*	Control group (n=8) *mean ± SD*	*p value*
SF-36				
PCS[#]	45 ± 6	46 ± 6	42 ± 5	*0.216*
MCS[#]	51 ± 7	55 ± 6	46 ± 6	*0.014**
Physical functioning[#]	59 ± 20	67 ± 14	52 ± 24	*0.154*
Role physical[#]	59 ± 23	72 ± 23	44 ± 14	*0.009**
Bodily pain[#]	65 ± 19	62 ± 12	63 ± 23	*0.910*
General health[#]	69 ± 19	72 ± 19	63 ± 19	*0.335*
Vitality[#]	59 ± 19	67 ± 18	52 ± 17	*0.116*
Social functioning[#]	75 ± 22	78 ± 22	69 ± 22	*0.417*
Role emotional[#]	73 ± 23	88 ± 17	57 ± 20	*0.003**
Mental health[#]	75 ± 16	80 ± 14	70 ± 18	*0.213*
FACT-L				
Physical well-being[#]	24 ± 4	25 ± 2	22 ± 5	*0.124*
Social/family well-being[#]	17 ± 9	20 ± 8	15 ± 9	*0.158*
Emotional well-being[#]	20 ± 4	21 ± 2	18 ± 5	*0.180*
Functional well-being[#]	17 ± 7	20 ± 5	13 ± 7	*0.045**
Lung cancer subscale[#]	18 ± 3	20 ± 3	16 ± 2	*0.006**
Total[#]	95 ± 21	106 ± 16	83 ± 22	*0.028**
EORTC QLQ-C30				
Global health status[#]	69 ± 20	74 ± 16	66 ± 24	*0.397*
Functional scales[#]	80 ± 14	85 ± 9	73 ± 16	*0.094*
Symptoms scales†	20 ± 10	20 ± 9	22 ± 11	*0.704*
EORTC LC13†	15 ± 9	16 ± 8	16 ± 9	*0.898*

Abbreviations: EORTC QLQ-C30 – The European organization for research and treatment of cancer, quality of life questionnaire core 30 version 3; EORTC LC13 – Lung cancer subscale of the EORTC QLQ-C30; FACT-L – The functional assessment of cancer therapy – lung scale, version 4; MCS – Mental component score; PCS – Physical component score; SD – Standard deviation; SF-36 – Medical outcomes study short form 36 general health survey.
[#]Greater scores reflect better outcome; †Lower scores reflect better outcome.
**Statistically significant difference between groups.*

Table 8-4: Baseline peripheral muscle force

Variable	**Total sample** *median [IQR]*	**Exercise group** *median [IQR]*	**Control group** *median [IQR]*	***p value***
Isometric quadriceps torque	***n = 12***	***n = 7***	***n = 5***	
Torque (Nm)	103 [90 to 187]	101 [66 to 145]	105 [94 to 226]	*0.465*
Torque (%pred)	99 [89 to 121]	103 [79 to 135]	97 [91 to 103]	*0.570*
Isometric handgrip force	***n = 17***	***n = 9***	***n = 8***	
Force (kg)	29 [20 to 33]	32 [20 to 34]	26 [20 to 30]	*0.357*
Force (%pred)	91 [84 to 111]	91 [83 to 111]	97 [83 to 111]	*0.885*

Abbreviation: IQR – Interquartile range.

8.5.1.5 Physical activity and sedentary behaviour

At baseline, the total number of days the activity monitors were worn by the participants was similar in both groups (6.6 ± 0.5 days [EG] *versus* 6.3 ± 1.1 days [CG]; $p = 0.49$). There were no differences between the EG and CG in any measure of physical activity or sedentary behaviour (Table 8-5).

8.5.1.6 Functional limitation resulting from dyspnoea and fatigue

At baseline, there was no difference between the EG and CG in their scores on the MMRC dyspnoea scale (Table 8-6). In the EG, seven participants (78%) reported a MMRC dyspnoea score of either 0 or 1 and two participants (22%) reported a MMRC dyspnoea score of 2. In the CG, five participants (62%) reported a MMRC dyspnoea score of either 0 or 1 and three participants (38%) reported a MMRC dyspnoea score of 2. The CG reported a lower score for the FACIT-Fatigue ($p < 0.01$) (Table 8-6).

8.5.1.7 Feelings of anxiety and depression

At baseline, there were no differences between the EG and CG in scores of anxiety and depression on the HADS (Table 8-6).

Table 8-5: Baseline physical activity and sedentary behaviour

Variable	Total sample (n=17) *mean ± SD*	Exercise group (n=9) *mean ± SD*	Control group (n=8) *mean ± SD*	*p value*
Monitors wear time (hr/day)	13.5 ± 1.2	13.7 ± 1.1	13.3 ± 1.4	*0.514*
Stepwatch activity monitor				
Daily steps	7920 ± 3552	9375 ± 3925	6282 ± 2331	*0.071*
SenseWear armband				
Sedentary behaviour (%)	68 ± 14	63 ± 15	74 ± 12	*0.104*
Light intensity PA (%)	21 ± 9	21 ± 10	20 ± 7	*0.752*
Moderate-to-vigorous intensity PA (%)	11 ± 11	16 ± 13	6 ± 6	*0.061*

Abbreviations: % - Percentage of waking hours; PA – Physical activity; SD – Standard deviation.
Definitions: Sedentary behaviour – energy expenditure < 1.5 metabolic equivalent units (METs); Light intensity PA – energy expenditure ≥ 1.5 and < 3 METs; Moderate-to-vigorous intensity PA – energy expenditure ≥ 3 METs.

Table 8-6: Baseline functional limitation resulting from dyspnoea, fatigue and feelings of anxiety and depression

Variable	**Total sample (n=17)** *median [IQR]*	**Exercise group (n=9)** *median [IQR]*	**Control group (n=8)** *median [IQR]*	***p value***
Dyspnoea				
MMRC†	1 [1 to 2]	1 [1 to 2]	1 [0 to 2]	*0.963*
Fatigue				
FACIT-Fatigue#	42 [37 to 46]	46 [43 to 49]	39 [26 to 40]	*0.004**
	mean ± SD	*mean ± SD*	*mean ± SD*	
Anxiety and depression				
HADS – anxiety score†	4 ± 3	3 ± 2	5 ± 3	*0.146*
HADS – depression score†	3 ± 3	2 ± 2	3 ± 3	*0.530*

Abbreviations: FACIT-Fatigue – Functional assessment of chronic illness therapy - fatigue subscale; HADS – The hospital anxiety and depression scale; IQR – Interquartile range; MMRC – Modified medical research council dyspnoea scale; SD – Standard deviation.
#Greater scores reflect better outcome; †Lower scores reflect better outcome.
**Statistically significant difference between groups.*

8.5.2 Phone calls (CG) and exercise training adherence (EG)

8.5.2.1 Phone calls (CG)

Of the eight participants who were randomised to the CG, three received a total of eight phone calls, one received six phone calls, two received five phone calls and two received four phone calls. The reasons for missing phone calls were that they were either away on vacation or busy with family-related issues. During the 8 weeks of follow up, one participant reported feeling unwell, and was subsequently diagnosed with a bone metastasis from NSCLC. Another participant developed a chest infection during the sixth week of follow-up and was treated with antibiotics for 7 days. After completion of the post-intervention assessment period all the eight participants in the CG were offered enrollment in the usual exercise training programmes at SCGH or RPH. Of these six (75%) declined.

8.5.2.2 Exercise training adherence (EG)

Of the nine participants who were randomised to the EG, four completed 15 or more sessions (i.e. $\geq$ 60% of the total number of sessions). The number of sessions attended by these four participants was 15, 17, 21 and 22. Of the remaining five participants, one attended 10 sessions and stopped training due to a diagnosis of pertussis. Two participants reported feeling unwell and stopped training after four and six sessions of exercise training. They completed some of the post-intervention assessments and were later diagnosed with a primary cancer other than lung cancer. One participant attended four sessions and decided to cease training stating they were too busy. The final participant declined exercise training as they were unwilling to travel to the hospital. In order to facilitate ITT analysis, all participants were encouraged to attend the post-intervention assessments, regardless of their adherence with the exercise training.

8.5.3 Progression in supervised exercises

Progression from the first to the last session of supervised exercise training was analysed for the eight participants of the EG who attended supervised exercise training.

8.5.3.1 Aerobic training

8.5.3.1.1 Walking

In the last session, the distance covered during the walking training was 11 ± 10% greater than in the first session (p = 0.02) (Table 8-7). There was no difference in walking speed (p = 0.14) (Table 8-7).

8.5.3.1.2 Cycle ergometer

Endurance training

In the last session, the product of work rate and cycling time during the cycle ergometer endurance training was 78 ± 35% greater than in the first session (p = 0.002) (Table 8-7).

Power training

There was no difference in the product of work rate and cycling time during the cycle ergometer power training (p = 0.08) (Table 8-7).

8.5.3.2 Resistance training

8.5.3.2.1 Lower limbs

In the last session, the number of step ups performed was 69 ± 46% greater than in the first session (p = 0.004) (Table 8-7).

8.5.3.2.2 Upper limbs

In the last session, the product of weights lifted, number of sets and number of repetitions during the biceps brachii muscle training was 53 ± 52% greater than in the first session (p = 0.02) (Table 8-7). There was no difference in the product of weights lifted, number of sets and number of repetitions during the deltoid muscle training (p = 0.08) (Table 8-7).

Table 8-7: Supervised exercise training progression

Variable	Exercise group (n=8) *mean ± SD*			*p value*
	First session	**Last session**	**MD [95% CI]**	
Aerobic training				
Walking training				
Distance (m)	1545 ± 353	1704 ± 338	159 [35 to 283]	*0.019**
Speed ($m \cdot min^{-1}$)	80 ± 14	84 ± 14	4 [-2 to 10]	*0.137*
Cycling training				
Endurance training				
Work rate·time (W·min)	222 ± 63	403 ± 164	181 [88 to 273]	*0.002**
Power training				
Work rate·time (W·min)	235 ± 63	250 ± 73	15 [-2 to 32]	*0.080*
Resistance training				
Lower limbs				
Number of step ups	30 ± 11	65 ± 28	35 [14 to 56]	*0.004**
Upper limbs				
Biceps (kg·sets·reps)	44 ± 8	66 ± 18	21 [4 to 38]	*0.022**
Deltoid (kg·sets·reps)	43 ± 10	49 ± 11	6 [-1 to 14]	*0.083*

Abbreviations: CI – Confidence interval; MD – Mean difference; SD – Standard deviation.
**Statistically significant difference.*

8.5.4 Post-intervention assessments completion

The number of participants in the EG and in the CG who completed each of the post-intervention assessments is presented in Figure 8-3.

8.5.5 Intention-to-treat analyses (without data imputation)

8.5.5.1 Primary outcomes

8.5.5.1.1 Exercise capacity

Cardiopulmonary exercise test

Within group differences:

In both the EG and CG, the duration of the CPET performed at baseline and post-intervention was similar (MD for EG [95% CI] 0.7 [-0.5 to 1.8] min; $p = 0.19$; MD for CG (MD [95% CI] -0.6 [-2.4 to 1.2] min; $p = 0.43$). In the EG, on completion of the intervention period, increases were observed in VO_{2peak} (%pred) ($p = 0.02$), oxygen pulse (O_2 pulse) ($p = 0.02$) and anaerobic threshold as a percentage of the VO_{2peak} (AT) ($p = 0.001$) (Table 8-8). There was also a trend for improvement in both VO_{2peak} ($L \cdot min^{-1}$) ($p = 0.06$) and VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) ($p = 0.06$). In the CG, on completion of the intervention period, a worsening in breathing reserve (BR) was observed ($p = 0.05$) (Table 8-8).

Between-group differences:

There was no between-group difference in the change in duration of the CPET performed at baseline and post-intervention (MD [95% CI] 1.3 [-0.8 to 3.4] min; $p = 0.20$). The increase in VO_{2peak} ($L \cdot min^{-1}$), VO_{2peak} (%pred), O_2 pulse and AT post-intervention in the EG was greater than any change in the CG (MD [95% CI] 0.19 [0.04 to 0.33] $L \cdot min^{-1}$; 10 [2 to 19]%pred; 2 [0 to 3] $ml \cdot beat^{-1}$; 11 [1 to 21]%, respectively; $p < 0.05$ for all) (Table 8-8).

Six-minute walk test

Within group differences:

Post-intervention, one participant of the CG required a rest of 38 seconds during the last minute of the 6MWT due to a combination of dyspnoea and leg fatigue (BORGd and BORGf = 7). None of the participants of the EG required a rest during the 6MWT. In the EG, on completion of the intervention period, increases were observed in 6MWD (m) ($p = 0.03$) and 6MWD (%pred) ($p = 0.01$) (Table 8-8). In the CG, on completion of the intervention period, no changes were seen in variables collected during the 6MWT (Table 8-8).

Between group differences:

Regarding between-group differences, the increase in 6MWD (m) and 6MWD (%pred) post-intervention in the EG was greater than any change in the CG (MD [95% CI] 52 [12 to 93] m; 9 [3 to 16]%pred; $p < 0.05$ for both) (Table 8-8).

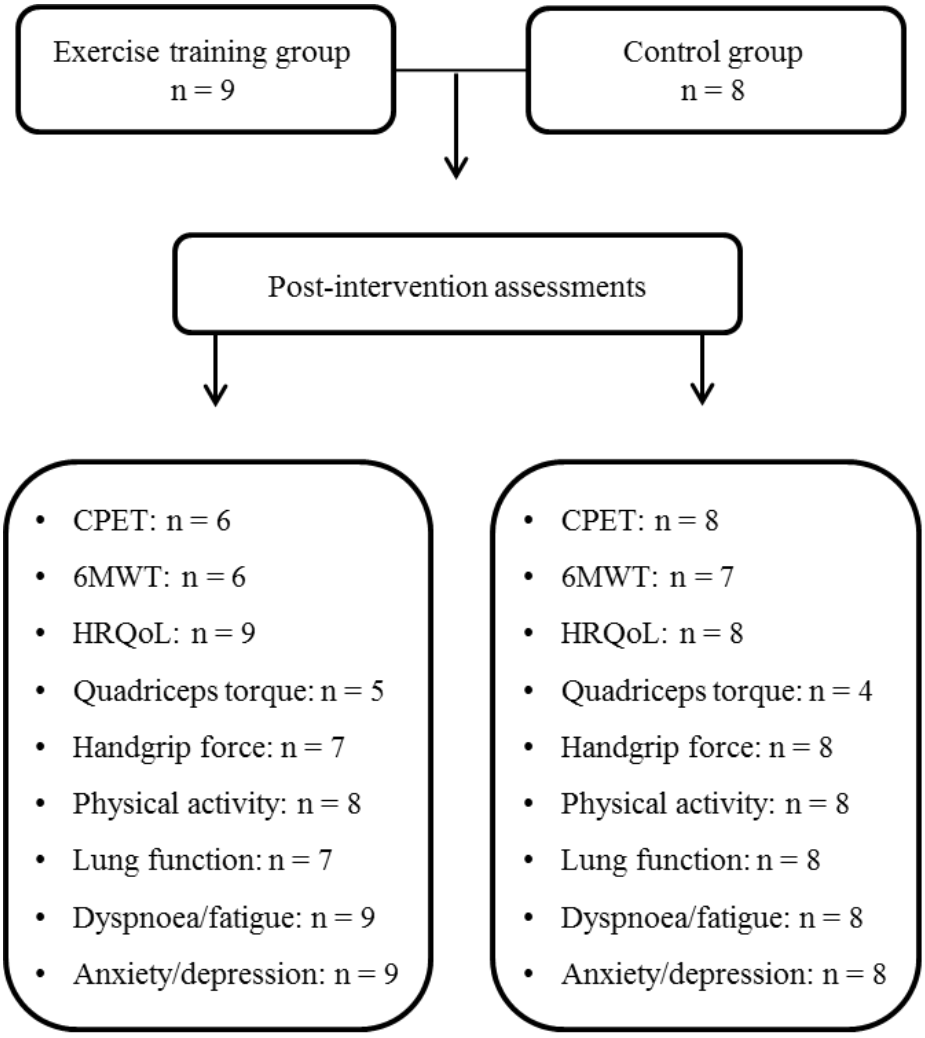

Figure 8-3: Number of participants who completed each of the post-intervention assessments.

Abbreviations: 6MWT – Six-minute walk test; CPET – Cardiopulmonary exercise test; HRQoL – Health-related quality of life.

Table 8-8: Baseline, post-intervention and within-group differences in measures of exercise capacity

Variable	Exercise group *mean ± SD*			Control group *mean ± SD*			*p value* *Between-group*
	Baseline	**Post-intervention**	**MD [95% CI]**	**Baseline**	**Post-intervention**	**MD [95% CI]**	
CPET	***n = 6***	***n = 6***		***n = 8***	***n = 8***		
VO_{2peak} ($L \cdot min^{-1}$)	0.96 ± 0.22	1.09 ± 0.28	0.14 [-0.01 to 0.28]	1.08 ± 0.40	1.03 ± 0.30	-0.05 [-0.15 to 0.05]	*0.020***
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	15.7 ± 3.1	17.0 ± 2.5	1.3 [-0.1 to 1.8]	13.9 ± 2.6	13.3 ± 2.1	-0.5 [-2.1 to 1.0]	*0.062*
VO_{2peak} (%pred)	62 ± 18	70 ± 21*	8 [2 to 15]	64 ± 17	62 ± 13	-2 [-9 to 5]	*0.021***
Wmax (W)	72 ± 22	77 ± 26	5 [-6 to 17]	77 ± 32	68 ± 21	-9 [-24 to 7]	*0.131*
Wmax (%pred)	73 ± 25	78 ± 30	6 [-4 to 15]	69 ± 15	64 ± 14	-5 [-18 to 8]	*0.182*
BORGd on completion CPET	6.8 ± 2.0	6.8 ± 1.7	0.0 [-3.1 to 3.1]	5.8 ± 3.0	6.1 ± 1.7	0.4 [-1.0 to 1.7]	*0.765*
BORGf on completion CPET	5.0 ± 2.5	6.8 ± 1.9	1.8 [-1.6 to 5.3]	7.4 ± 2.1	6.9 ± 2.0	-0.5 [-3.1 to 2.1]	*0.205*
Nadir SpO_2 (%)	94 ± 2	94 ± 4	1 [-4 to 5]	94 ± 6	95 ± 3	1 [-6 to 7]	*0.991*
HRmax (bpm)	130 ± 20	124 ± 19	-6 [-13 to 2]	127 ± 18	128 ± 18	1 [-15 to 17]	*0.438*
BR (%)	27 ± 12	28 ± 13	1 [-14 to 16]	32 ± 14	43 ± 10*	11 [0 to 23]	*0.187*
O_2 pulse ($ml \cdot beat^{-1}$)	7 ± 2	9 ± 2*	2 [0 to 2]	8 ± 3	8 ± 3	0 [-1 to 1]	*0.013***
AT (%VO_{2peak})	60 ± 9	71 ± 8*	11 [7 to 15]	63 ± 10	63 ± 10	7 [2 to 13]	*0.034***
VEmax/MVV (%)	73 ± 12	72 ± 13	-1 [-16 to 14]	68 ± 14	58 ± 12	-9 [-20 to 1]	*0.143*
6MWT	***n = 6***	***n = 6***		***n = 7***	***n = 7***		
6MWD (m)	540 ± 71	585 ± 77*	45 [6 to 83]	477 ± 78	469 ± 105	-8 [-36 to 20]	*0.016***
6MWD (%pred)	88 ± 9	96 ± 5*	8 [3 to 14]	77 ± 11	76 ± 16	-1 [-6 to 4]	*0.012***
BORGd on completion 6MWT	3.3 ± 2.0	2.8 ± 1.2	-0.5 [-2.5 to 1.5]	3.4 ± 1.5	3.7 ± 2.4	0.3 [-1.2 to 1.9]	*0.245*
BORGf on completion 6MWT	1.5 ± 1.9	2.3 ± 1.8	0.8 [-1.3 to 2.8]	3.4 ± 1.9	4.1 ± 1.6	0.7 [-1.2 to 2.6]	*0.804*
Nadir SpO_2 (%)	92 ± 4	92 ± 3	0 [-2 to 1]	92 ± 2	93 ± 1	1 [0 to 2]	*0.399*
Peak HR (bpm)	125 ± 16	126 ± 15	1 [-13 to 15]	122 ± 11	121 ± 18	0 [-9 to 8]	*0.975*

Abbreviations: 6MWD – Six-minute walk distance; 6MWT – Six-minute walk test; AT – Anaerobic threshold as a percentage of the VO_{2peak}; BORGd – Dyspnoea; BORGf – Fatigue; BR – Breathing reserve; CI – Confidence interval; CPET – Cardiopulmonary exercise test; HR – Heart rate; HRmax – Maximal heart rate; MD – Mean difference; O_2 pulse – Oxygen pulse; SD – Standard deviation; SpO_2 - Arterial oxygen saturation measured via pulse oximetry; VEmax/MVV – Maximum minute ventilation, maximum voluntary ventilation ratio; VO_{2peak} – Peak rate of oxygen consumption; Wmax – Maximum work rate.
Statistically significant difference from baseline to post-intervention; Statistically significant difference in MD between groups.*

8.5.5.1.2 Health-related quality of life

Medical outcomes study short form 36 general health survey

On completion of the intervention period, no within or between-group differences were observed in either the component summary scores or individual domains of the SF-36 (Table 8-9).

The functional assessment of cancer therapy – lung scale, version 4

In the EG, on completion of the intervention period, the score on the lung cancer subscale of the FACT-L increased ($p = 0.04$) (Table 8-9), indicating improved HRQoL. In the CG, on completion of intervention period, the score of both social/family well-being and the lung cancer subscale of the FACT-L increased ($p < 0.05$ for both) (Table 8-9), indicating improved HRQoL.

No between-group differences on baseline-to-post-intervention change in scores of the subscales of the FACT-L were demonstrated (Table 8-9).

The European organisation for research and treatment of cancer, quality of life questionnaire core 30, version 3

On completion of the intervention period, no within or between-group differences were observed in scores of the EORTC QLQ-C30 (Table 8-9).

8.5.5.1.3 Peripheral muscle force

Isometric quadriceps torque and isometric handgrip force

On completion of the intervention period, no within or between-group differences were observed in isometric quadriceps torque or isometric handgrip force (Table 8-10).

Table 8-9: Baseline, post-intervention and within-group differences in measures of health-related quality of life

Variable	Exercise group (n=9) *mean ± SD*			Control group (n=8) *mean ± SD*			*p value*
	Baseline	Post-intervention	MD [95% CI]	Baseline	Post-intervention	MD [95% CI]	*Between-group*
SF-36							
PCS#	46 ± 6	48 ± 8	2 [-3 to 6]	42 ± 5	40 ± 9	-2 [-7 to 2]	*0.164*
MCS#	55 ± 6	51 ± 14	-4 [-12 to 5]	46 ± 6	51 ± 8	5 [-2 to 12]	*0.200*
Physical functioning#	67 ± 14	74 ± 18	7 [-4 to 18]	52 ± 24	55 ± 23	3 [-8 to 13]	*0.488*
Role physical#	72 ± 23	69 ± 38	-3 [-22 to 17]	44 ± 14	44 ± 17	0 [-16 to 16]	*0.834*
Bodily pain#	62 ± 12	60 ± 26	-2 [-26 to 22]	63 ± 23	56 ± 33	-8 [-34 to 19]	*0.713*
General health#	72 ± 19	72 ± 26	0 [-15 to 14]	63 ± 19	65 ± 21	3 [-13 to 18]	*0.728*
Vitality#	67 ± 18	72 ± 30	5 [-10 to 20]	52 ± 17	54 ± 17	2 [-7 to 10]	*0.668*
Social functioning#	78 ± 22	74 ± 35	-4 [-21 to 13]	69 ± 22	73 ± 29	5 [-15 to 25]	*0.438*
Role emotional#	88 ± 17	80 ± 29	-8 [-31 to 14]	57 ± 20	68 ± 22	10 [-10 to 31]	*0.968*
Mental health#	80 ± 14	73 ± 24	-7 [-23 to 9]	70 ± 18	79 ± 17	9 [-3 to 20]	*0.094*
FACT-L							
Physical well-being#	25 ± 2	24 ± 5	-1 [-4 to 3]	22 ± 5	21 ± 7	-1 [-4 to 2]	*0.907*
Social/family well-being#	20 ± 8	21 ± 7	0 [-4 to 4]	15 ± 9	19 ± 6*	4 [1 to 8]	*0.087*
Emotional well-being#	21 ± 2	19 ± 6	-2 [-5 to 1]	18 ± 5	20 ± 4	2 [-1 to 5]	*0.077*
Functional well-being#	20 ± 5	21 ± 9	2 [-3 to 6]	13 ± 7	17 ± 8	4 [-5 to 12]	*0.786*
Lung cancer subscale#	20 ± 3	22 ± 4*	3 [0 to 5]	16 ± 2	20 ± 3*	5 [1 to 8]	*0.694*
Total#	106 ± 16	107 ± 25	2 [-10 to 14]	83 ± 22	97 ± 21	13 [-1 to 28]	*0.344*
EORTC QLQ-C30							
Global health status#	74 ± 16	75 ± 25	1 [-22 to 24]	66 ± 24	64 ± 22	-2 [-10 to 6]	*0.780*
Functional scales#	85 ± 9	85 ± 17	0 [-10 to 11]	73 ± 16	76 ± 12	3 [-3 to 9]	*0.626*
Symptoms scales†	20 ± 9	17 ± 13	-3 [-15 to 8]	22 ± 11	23 ± 15	1 [-8 to 10]	*0.507*
EORTC LC13†	16 ± 8	14 ± 8	-2 [-10 to 6]	16 ± 9	25 ± 19	9 [-1 to 19]	*0.064*

Abbreviations: CI – Confidence interval; EORTC QLQ-C30 – The European organization for research and treatment of cancer, quality of life questionnaire core 30 version 3; EORTC LC13 – Lung cancer subscale of the EORTC QLQ-C30; FACT-L – The functional assessment of cancer therapy – lung scale, version 4; MCS – Mental component score; MD – Mean difference; PCS – Physical component score; SD – Standard deviation; SF-36 – Medical outcomes study short form 36 general health survey.
#Greater scores reflect better outcome; †Lower scores reflect better outcome.
**Statistically significant difference from baseline to post-intervention.*

Table 8-10: Baseline, post-intervention and within-group differences in measures of peripheral muscle force

Variable	Exercise group *median [IQR]*		Control group *median [IQR]*		*p value* *Between-group*
	Baseline	**Post-intervention**	**Baseline**	**Post-intervention**	
Isometric quadriceps torque	***n = 5***	***n = 5***	***n = 4***	***n = 4***	
Torque (Nm)	101 [70 to 132]	112 [82 to 142]	151 [91 to 238]	153 [101 to 210]	*0.556*
Torque (%pred)	103 [87 to 160]	114 [100 to 171]	99 [93 to 104]	97 [82 to 114]	*0.190*
Isometric handgrip force	***n = 7***	***n = 7***	***n = 8***	***n = 8***	
Force (kg)	32 [18 to 34]	33 [20 to 35]	26 [20 to 30]	26 [19 to 31]	*0.072*
Force (%pred)	91 [78 to 115]	93 [78 to 127]	97 [83 to 111]	100 [83 to 107]	*0.281*

Abbreviation: IQR – Interquartile range.

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8.5.5.1.4 Physical activity and sedentary behaviour

On completion of the intervention period, no within-group difference in the number of days the monitors were worn was observed (MD for EG [95% CI] 0 [-1 to 1] days; $p = 0.73$; MD for CG (MD [95% CI] 0 [-1 to 1] days; $p = 0.35$). On completion of the intervention period, no within or between-group differences were observed in any measures of physical activity and sedentary behaviour (Table 8-11).

8.5.5.2 Secondary outcomes

8.5.5.2.1 Lung function

On completion of the intervention period, no within or between-group differences were observed in any measures of lung function (Table 8-12).

8.5.5.2.2 Functional limitation resulting from dyspnoea and fatigue

On completion of the intervention period, no within or between-group differences were observed in the MMRC dyspnoea score or the FACIT-Fatigue scores (Table 8-13).

8.5.5.2.3 Feelings of anxiety and depression

On completion of the intervention period, no within or between-group differences were observed in the anxiety and depression scores measured using the HADS (Table 8-13).

Table 8-11: Baseline, post-intervention and within-group differences in measures of physical activity and sedentary behaviour

Variable	Exercise group (n=8) *mean ± SD*			Control group (n=8) *mean ± SD*			*p value*
	Baseline	Post-intervention	MD [95% CI]	Baseline	Post-intervention	MD [95% CI]	*Between-group*
Monitors wear time (hr/day)	13.8 ± 1.2	13.0 ± 1.1	-0.8 [-2.0 to 0.4]	13.3 ± 1.4	13.2 ± 1.5	-0.4 [-1.3 to 0.5]	*0.105*
Stepwatch activity monitor							
Daily steps	9357 ± 4195	9816 ± 4382	460 [-153 to 1073]	6282 ± 2331	8020 ± 3864	1738 [-455 to 3931]	*0.206*
SenseWear armband							
Sedentary behaviour (%)	62 ± 16	59 ± 16	-3 [-7 to 1]	74 ± 12	67 ± 14	-7 [-13 to 1]	*0.312*
Light intensity PA (%)	21 ± 11	25 ± 11	4 [-3 to 11]	20 ± 7	26 ± 11	6 [-1 to 12]	*0.582*
Moderate-to-vigorous intensity PA (%)	17 ± 13	16 ± 8	-1 [-6 to 4]	6 ± 6	7 ± 4	1 [-3 to 5]	*0.599*

Abbreviations: % - Percentage of waking hours; CI – Confidence interval; MD – Mean difference; PA – Physical activity; SD – Standard deviation.
Definitions: Sedentary behaviour – energy expenditure < 1.5 metabolic equivalent units (METs); Light intensity PA – energy expenditure ≥ 1.5 and < 3 METs; Moderate-to-vigorous intensity PA – energy expenditure ≥ 3 METs.

Table 8-12: Baseline, post-intervention and within-group differences in measures of lung function

Variable	Exercise group (n=7) *mean ± SD*			Control group (n=8) *mean ± SD*			***p value***
	Baseline	**Post-intervention**	**MD [95% CI]**	**Baseline**	**Post-intervention**	**MD [95% CI]**	*Between-group*
FEV_1 (L)	1.50 ± 0.54	1.54 ± 0.56	0.04 [-0.04 to 0.11]	1.78 ± 0.50	1.90 ± 0.55	0.12 [-0.02 to 0.23]	*0.140*
FEV_1 (%pred)	62 ± 19	64 ± 23	2 [-2 to 7]	71 ± 15	76 ± 16	5 [-1 to 9]	*0.245*
FVC (L)	2.54 ± 0.87	2.54 ± 0.74	0.00 [-0.22 to 0.23]	2.87 ± 0.58	2.99 ± 0.78	0.12 [-0.11 to 0.37]	*0.398*
FVC (%pred)	77 ± 10	78 ± 10	1 [-5 to 7]	86 ± 10	89 ± 15	4 [-3 to 10]	*0.539*
FEV_1/FVC (%)	60 ± 15	61 ± 16	1 [-3 to 4]	62 ± 11	64 ± 9	2 [-2 to 6]	*0.582*
TLC (L)	4.52 ± 1.75	4.64 ± 1.49	0.12 [-0.41 to 0.66]	4.91 ± 0.64	5.05 ± 0.86	0.15 [-0.25 to 0.54]	*0.901*
TLC (%pred)	83 ± 16	87 ± 15	4 [-6 to 13]	90 ± 12	93 ± 16	3 [-5 to 10]	*0.850*
FRC (L)	2.86 ± 1.10	3.01 ± 1.01	0.16 [-0.18 to 0.49]	3.02 ± 0.47	2.98 ± 0.67	-0.04 [-0.34 to 0.27]	*0.344*
FRC (%pred)	95 ± 19	102 ± 22	7 [-6 to 19]	100 ± 21	99 ± 25	-1 [-12 to 9]	*0.270*
D_LCO ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	12.2 ± 3.0	11.2 ± 2.5	-1.0 [-2.2 to 0.1]	14.7 ± 3.8	15.1 ± 4.5	0.4 [-1.4 to 2.1]	*0.147*
D_LCO (%pred)	48 ± 8	44 ± 8	-4 [-8 to 0]	57 ± 13	58 ± 12	1 [-6 to 8]	*0.204*
MVV ($L \cdot min^{-1}$)	60 ± 25	62 ± 22	4 [-5 to 12]	64 ± 28	70 ± 18	6 [0 to 12]	*0.605*
MVV (%pred)	58 ± 27	62 ± 24	5 [-5 to 15]	67 ± 18	73 ± 12	5 [0 to 11]	*0.971*

Abbreviations: CI – Confidence interval; D_LCO – Single breath diffusing capacity for carbon monoxide; FEV_1 – Forced expiratory volume in one second; FRC – Functional residual capacity; FVC – Forced vital capacity; MD – Mean difference; MVV – Maximum voluntary ventilation; SD – Standard deviation; TLC – Total lung capacity.

Table 8-13: Baseline, post-intervention and within-group differences in measures of functional limitation resulting from dyspnoea, fatigue and feelings of anxiety and depression

Variable	Exercise group (n=9) *median [IQR]*		Control group (n=8) *median [IQR]*		*p value* *Between-group*
	Baseline	**Post-intervention**	**Baseline**	**Post-intervention**	
Dyspnoea					
MMRC†	1 [1 to 2]	1 [0 to 2]	1 [0 to 2]	1 [0 to 2]	*0.773*
Fatigue					
FACIT-Fatigue#	46 [43 to 49]	47 [38 to 52]	39 [26 to 40]	38 [28 to 42]	*0.815*

Variable	Exercise group (n=9) *mean ± SD*			Control group (n=8) *mean ± SD*			*p value* *Between-group*
	Baseline	**Post-intervention**	**MD [95% CI]**	**Baseline**	**Post-intervention**	**MD [95% CI]**	
Anxiety and depression							
HADS – anxiety score†	3 ± 2	5 ± 4	2 [-1 to 5]	5 ± 3	5 ± 4	-1[-3 to 2]	*0.174*
HADS – depression score†	2 ± 2	4 ± 5	2 [-1 to 4]	3 ± 3	4 ± 3	0 [-1 to 1]	*0.400*

Abbreviations: CI – Confidence interval; FACIT-Fatigue – Functional assessment of chronic illness therapy - fatigue subscale; HADS – The hospital anxiety and depression scale; IQR – Interquartile range; MD – Mean difference; MMRC – Modified medical research council dyspnoea scale; SD – Standard deviation.
#Greater scores reflect better outcome; †Lower scores reflect better outcome.

8.5.6 Intention-to-treat analyses (BOCF)

8.5.6.1 Primary outcomes

8.5.6.1.1 Exercise capacity

Cardiopulmonary exercise test

Within group differences:

In both the EG and CG, the duration of the CPET performed at baseline and post-intervention were similar (MD for EG [95% CI] 0.5 [-0.3 to 1.2] min; $p = 0.18$; MD for CG [95% CI] -0.6 [-2.4 to 1.2] min; $p = 0.43$). In the EG, on completion of the intervention period, increases were observed in VO_{2peak} (%pred) ($p = 0.03$), O_2 pulse ($p = 0.03$) and AT ($p = 0.01$) (Table 8-14). There was also a trend for improvement in both VO_{2peak} ($L \cdot min^{-1}$) ($p = 0.07$) and VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) ($p = 0.06$). In the CG, on completion of the intervention period, a worsening in BR was observed ($p = 0.05$) (Table 8-14).

Between-group differences:

There was no between-group difference in the change in duration of the CPET performed at baseline and post-intervention (MD [95% CI] 1.1 [-0.6 to 2.8] min; $p = 0.18$). The increase in VO_{2peak} ($L \cdot min^{-1}$), VO_{2peak} (%pred) and O_2 pulse following intervention in the EG was greater than any change in the CG (MD [95% CI] 0.14 [0.01 to 0.27] $L \cdot min^{-1}$; 8 [1 to 15]%pred; 1 [0 to 2] $ml \cdot beat^{-1}$, respectively; $p < 0.05$ for all) (Table 8-14).

Six-minute walk test

Within group differences:

Post-intervention, one participant in the CG required a rest of 38 seconds during the last minute of the 6MWT due to a combination of dyspnoea and leg fatigue (BORGd and BORGf = 7). None of the participants of the EG required a rest during the 6MWT. In the EG, on completion of the intervention period, increases were observed in 6MWD (m) ($p = 0.04$) and 6MWD (%pred) ($p = 0.03$) (Table 8-14). In the CG, on

completion of the intervention period, no changes were seen in variables collected during the 6MWT (Table 8-14).

Between group differences:

Regarding between-group differences, the increase in 6MWD (m) and in 6MWD (%pred) post-intervention in the EG was greater than any change in the CG (MD [95% CI] 36 [3 to 70] m; 6 [1 to 12]%pred; $p < 0.05$ for both) (Table 8-14).

8.5.6.1.2 Health-related quality of life

All participants in the EG and CG completed the three HRQoL questionnaires following the intervention period. Therefore, the results of the ITT analyses without data imputation are those presented earlier in this Chapter (heading 8.5.5.1.2 Health-related quality of life; and Table 8-9).

Table 8-14: Baseline, post-intervention and within-group differences in measures of exercise capacity (BOCF)

Variable	Exercise group (n=9) *mean ± SD*			Control group (n=8) *mean ± SD*			*p value*
	Baseline	Post-intervention	MD [95% CI]	Baseline	Post-intervention	MD [95% CI]	*Between-group*
CPET							
VO_{2peak} ($L \cdot min^{-1}$)	1.01 ± 0.22	1.10 ± 0.24	0.09 [-0.01 to 0.19]	1.08 ± 0.40	1.03 ± 0.30	-0.05 [-0.15 to 0.05]	*0.037***
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	15.3 ± 3.2	16.2 ± 3.0	0.9 [-0.1 to 1.8]	13.9 ± 2.6	13.3 ± 2.1	-0.5 [-2.1 to 1.0]	*0.083*
VO_{2peak} (%pred)	60 ± 16	65 ± 20*	6 [1 to 10]	64 ± 17	62 ± 13	-2 [-9 to 5]	*0.048***
Wmax (W)	71 ± 20	75 ± 23	4 [-3 to 11]	77 ± 32	68 ± 21	-9 [-24 to 7]	*0.103*
Wmax (%pred)	69 ± 22	73 ± 26	4 [-2 to 10]	69 ± 15	64 ± 14	-5 [-18 to 8]	*0.177*
BORGd on completion CPET	6.9 ± 2.4	6.9 ± 2.2	0.0 [-1.8 to 1.8]	5.8 ± 3.0	6.1 ± 1.7	0.4 [-1.0 to 1.7]	*0.709*
BORGf on completion CPET	5.6 ± 2.3	6.8 ± 1.7	1.2 [-0.9 to 3.4]	7.4 ± 2.1	6.9 ± 2.0	-0.5 [-3.1 to 2.1]	*0.250*
Nadir SpO_2 (%)	94 ± 2	95 ± 3	1 [-1 to 1]	94 ± 6	95 ± 3	1 [-6 to 7]	*0.912*
HRmax (bpm)	127 ± 19	123 ± 18	-4 [-8 to 1]	127 ± 18	128 ± 18	1 [-15 to 17]	*0.487*
BR (%)	25 ± 16	20 ± 16	-5 [-20 to 11]	32 ± 14	43 ± 10*	11 [0 to 23]	*0.094*
O_2 pulse ($ml \cdot beat^{-1}$)	8 ± 2	9 ± 2*	1 [0 to 2]	8 ± 3	8 ± 3	0 [-1 to 1]	*0.033***
AT (%VO_{2peak})	62 ± 9	69 ± 9*	7 [2 to 13]	63 ± 10	63 ± 10	7 [2 to 13]	*0.103*
VEmax/MVV (%)	75 ± 17	75 ± 17	0 [-10 to 8]	68 ± 14	58 ± 12	-9 [-20 to 1]	*0.084*
6MWT							
6MWD (m)	521 ± 75	551 ± 89*	30 [2 to 58]	480 ± 73	473 ± 98	-7 [-30 to 17]	*0.036***
6MWD (%pred)	83 ± 11	89 ± 12*	6 [1 to 10]	77 ± 10	76 ± 15	-1 [-5 to 4]	*0.033***
BORGd on completion 6MWT	3.4 ± 1.7	3.1 ± 1.2	-0.3 [-1.5 to 0.8]	3.3 ± 1.4	3.6 ± 2.3	0.3 [-1.0 to 1.6]	*0.394*
BORGf on completion 6MWT	1.4 ± 1.7	1.9 ± 1.7	0.5 [-0.7 to 1.7]	3.0 ± 1.4	3.7 ± 1.9	0.6 [-1.0 to 2.2]	*0.886*
Nadir SpO_2 (%)	92 ± 3	92 ± 3	0 [-1 to 1]	92 ± 2	93 ± 1	1 [0 to 2]	*0.196*
Peak HR (bpm)	123 ± 13	124 ± 12	-4 [-9 to 1]	121 ± 10	121 ± 17	0 [-7 to 7]	*0.805*

Abbreviations: 6MWD – Six-minute walk distance; 6MWT – Six-minute walk test; AT – Anaerobic threshold as a percentage of the VO_{2peak}; BOCF – Baseline–observation-carried-forward; BORGd – Dyspnoea; BORGf – Fatigue; BR – Breathing reserve; CI – Confidence interval; CPET – Cardiopulmonary exercise test; HR – Heart rate; HRmax – Maximal heart rate; MD – Mean difference; O_2 pulse – Oxygen pulse; SD – Standard deviation; SpO_2 - Arterial oxygen saturation measured via pulse oximetry; VEmax/MVV – Maximum minute ventilation, maximum voluntary ventilation ratio; VO_{2peak} – Peak rate of oxygen consumption; Wmax – Maximum work rate.

Statistically significant difference from baseline to post-intervention; Statistically significant difference in MD between groups.*

8.5.6.1.3 Peripheral muscle force

Isometric quadriceps torque and isometric handgrip force

On completion of the intervention period, no within or between-group differences were observed in isometric quadriceps torque or isometric handgrip force (Table 8.15)

8.5.6.1.4 Physical activity and sedentary behaviour

On completion of the intervention period, no within-group difference in number of days the monitors were worn was observed (MD for EG [95% CI] 0 [-1 to 1] days; $p = 0.73$; MD for CG (MD [95% CI] 0 [-1 to 1] days; $p = 0.35$). On completion of the intervention period, no within or between-group differences were observed in any measures of physical activity and sedentary behaviour (Table 8-16).

8.5.6.2 Secondary outcomes

8.5.6.2.1 Lung function

On completion of the intervention period, no within or between-group differences were observed in any measures of lung function (Table 8-17).

8.5.6.2.2 Functional limitation resulting from dyspnoea and fatigue

All the participants from the EG and CG completed the MMRC dyspnoea scale and the FACIT-Fatigue following the intervention period. Therefore, the results of the ITT analyses without data imputation are those presented earlier in this Chapter (heading 8.5.6.2.2 Functional limitation resulting from dyspnoea and fatigue; and Table 8-13).

8.5.6.2.3 Feelings of anxiety and depression

All the participants from the EG and CG completed the HADS following the intervention period. Therefore, the results of the ITT analyses without data imputation are those presented earlier in this Chapter (heading 8.5.5.2.3 Feelings of anxiety and depression; and Table 8-13).

Table 8-15: Baseline, post-intervention and within-group differences in measures of peripheral muscle force (BOCF)

Variable	Exercise group *median [IQR]*		Control group *median [IQR]*		*p value* *Between-group*
	Baseline	**Post-intervention**	**Baseline**	**Post-intervention**	
Isometric quadriceps torque	***n = 7***	***n = 7***	***n = 5***	***n = 5***	
Torque (Nm)	101 [66 to 145]	112 [66 to 146]	105 [94 to 226]	105 [102 to 208]	*0.755*
Torque (%pred)	103 [79 to 135]	114 [99 to 135]	97 [91 to 103]	93 [84 to 110]	*0.432*
Isometric handgrip force	***n = 9***	***n = 9***	***n = 8***	***n = 8***	
Force (kg)	32 [20 to 34]	32 [21 to 34]	26 [20 to 30]	26 [19 to 31]	*0.114*
Force (%pred)	91 [83 to 111]	91 [83 to 118]	97 [83 to 111]	100 [83 to 107]	*0.351*

Abbreviation: BOCF – Baseline–observation-carried-forward; IQR – Interquartile range.

Table 8-16: Baseline, post-intervention and within-group differences in measures of physical activity and sedentary behaviour (BOCF)

Variable	Exercise group (n=9) *mean ± SD*			Control group (n=8) *mean ± SD*			***p value***
	Baseline	**Post-intervention**	**MD [95% CI]**	**Baseline**	**Post-intervention**	**MD [95% CI]**	*Between-group*
Monitors wear time (hr/day)	13.7 ± 1.1	13.0 ± 1.0	-0.7 [-1.7 to 0.3]	13.3 ± 1.4	13.2 ± 1.5	-0.4 [-1.3 to 0.5]	*0.136*
Stepwatch activity monitor							
Daily steps	9375 ± 3925	9784 ± 4100	408 [-131 to 949]	6282 ± 2331	8020 ± 3864	1738 [-455 to 3931]	*0.163*
SenseWear armband							
Sedentary behaviour (%)	63 ± 15	60 ± 15	-3 [-6 to 1]	74 ± 12	67 ± 14	-7 [-13 to 1]	*0.246*
Light intensity PA (%)	21 ± 10	25 ± 10	4 [-2 to 9]	20 ± 7	26 ± 11	6 [-1 to 12]	*0.485*
Moderate-to-vigorous intensity PA (%)	16 ± 13	15 ± 9	-1 [-6 to 4]	6 ± 6	7 ± 4	1 [-3 to 5]	*0.603*

Abbreviations: % - Percentage of waking hours; BOCF – Baseline–observation-carried-forward; CI – Confidence interval; MD – Mean difference; PA – Physical activity; SD – Standard deviation.
Definitions: Sedentary behaviour – energy expenditure < 1.5 metabolic equivalent units (METs); Light intensity physical activity – energy expenditure ≥ 1.5 and < 3 METs; Moderate-to-vigorous intensity physical activity – energy expenditure ≥ 3 METs.

Table 8-17: Baseline, post-intervention and within-group differences in measures of lung function (BOCF)

Variable	Exercise group (n=9) *mean ± SD*			Control group (n=8) *mean ± SD*			***p value***
	Baseline	**Post-intervention**	**MD [95% CI]**	**Baseline**	**Post-intervention**	**MD [95% CI]**	*Between-group*
FEV_1 (L)	1.53 ± 0.47	1.55 ± 0.49	0.03 [-0.03 to 0.08]	1.78 ± 0.50	1.90 ± 0.55	0.12 [-0.02 to 0.23]	*0.068*
FEV_1 (%pred)	61 ± 17	63 ± 20	2 [-2 to 5]	71 ± 15	76 ± 16	5 [-1 to 9]	*0.130*
FVC (L)	2.51 ± 0.76	2.51 ± 0.66	0.00 [-0.16 to 0.17]	2.87 ± 0.58	2.99 ± 0.78	0.12 [-0.11 to 0.37]	*0.334*
FVC (%pred)	74 ± 11	75 ± 11	1 [-4 to 5]	86 ± 10	89 ± 15	4 [-3 to 10]	*0.617*
FEV_1/FVC (%)	62 ± 14	63 ± 15	1 [-2 to 3]	62 ± 11	64 ± 9	2 [-2 to 6]	*0.477*
TLC (L)	4.58 ± 1.56	4.67 ± 1.33	0.09 [-0.29 to 0.48]	4.91 ± 0.64	5.05 ± 0.86	0.15 [-0.25 to 0.54]	*0.794*
TLC (%pred)	82 ± 16	85 ± 16	3 [-4 to 10]	90 ± 12	93 ± 16	3 [-5 to 10]	*0.973*
FRC (L)	2.87 ± 1.00	2.99 ± 0.93	0.12 [-0.12 to 0.37]	3.02 ± 0.47	2.98 ± 0.67	-0.04 [-0.34 to 0.27]	*0.384*
FRC (%pred)	94 ± 20	99 ± 23	5 [-4 to 15]	100 ± 21	99 ± 25	-1 [-12 to 9]	*0.307*
D_LCO ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	12.8 ± 3.3	12.0 ± 3.3	-0.8 [-1.7 to 0.1]	14.7 ± 3.8	15.1 ± 4.5	0.4 [-1.4 to 2.1]	*0.167*
D_LCO (%pred)	49 ± 11	46 ± 11	-3 [-6 to 0]	57 ± 13	58 ± 12	1 [-6 to 8]	*0.233*
MVV ($L \cdot min^{-1}$)	60 ± 25	62 ± 22	3 [-3 to 9]	64 ± 28	70 ± 18	6 [0 to 12]	*0.428*
MVV (%pred)	59 ± 15	63 ± 17	4 [-3 to 11]	67 ± 18	73 ± 12	5 [0 to 11]	*0.752*

Abbreviations: BOCF – Baseline–observation-carried-forward; CI – Confidence interval; D_LCO – Single breath diffusing capacity for carbon monoxide; FEV_1 – Forced expiratory volume in one second; FRC – Functional residual capacity; FVC – Forced vital capacity; MD – Mean difference; MVV – Maximum voluntary ventilation; SD – Standard deviation; TLC – Total lung capacity.

8.5.7 Exercise training effects (participants who adhered to exercise training)

Results of the four participants from the EG group who were considered adherent to the exercise training programme (i.e. completed at least 15 sessions [≥ 60% of the total number of sessions]) are presented in this section.

Participant 3 was the only person who chose to attend two supervised sessions of exercise training per week and, thus, was provided with a cycle ergometer at home to complete one extra training session per week.

Regarding the number of sessions completed, participant 1 attended 15 supervised sessions; participant 2 attended 17 supervised sessions; participant 3 attended 15 supervised sessions and completed 6 exercise sessions at home (i.e. a total of 21 sessions) and; participant 4 attended 22 supervised sessions.

8.5.7.1 Primary outcomes

8.5.7.1.1 Exercise capacity

Cardiopulmonary exercise test

The work rate increments used for participants 1, 2, 3 and 4 were 5, 7.5, 7.5 and 12 W, respectively. The duration of the CPET at baseline was 13.6, 8.3, 8.9 and 8.0 minutes, respectively. Post-intervention, the duration of the CPET was 14.8, 8.3, 10.5 and 9.9 minutes, respectively. Figure 8-4 displays the baseline and post-intervention measures of VO_{2peak} ($L \cdot min^{-1}$) and Wmax for each of the four participants. Compared with the baseline VO_{2peak}, the post-intervention VO_{2peak} ($L \cdot min^{-1}$) for participants 1, 2, 3 and 4 increased by 19, 13, 15 and 33%, respectively. Participants 1, 2 and 4 improved their Wmax by 9, 18 and 24%, whereas the Wmax of Participant 3 remained unchanged. Changes in other variables collected during the baseline and post-intervention CPET, for each of the four participants, are presented in Table 8-18.

Six-minute walk test

Figure 8-5 displays the baseline and post-intervention 6MWD (m) for each participant. Compared with the baseline 6MWD, the post-intervention 6MWD for

participants 1, 3 and 4 increased by 15, 8 and 17%, respectively. The post-intervention 6MWD of participant 2 was 3% lower than the baseline 6MWD. Changes in other variables collected during the baseline and post-intervention 6MWT, for each of the four participants, are presented in Table 8-18.

8.5.7.1.2 Health-related quality of life

Medical outcomes study short form 36 general health survey

Compared to baseline values, the four participants presented improved scores at the post-intervention assessment in both PCS and MCS of the SF-36 (Table 8-19). In general, the four participants also presented either higher or similar scores for the eight domains of the SF-36 (Table 8-19).

The functional assessment of cancer therapy – lung scale, version 4

Compared to the baseline value, the four participants presented greater post-intervention total score of the FACT-L (Table 8-19). In general, the four participants also presented either higher or similar scores for the five subscales of the FACT-L (Table 8-19).

The European organisation for research and treatment of cancer, quality of life questionnaire core 30, version 3

Compared to baseline values, the four participants presented either improved or similar scores post-intervention for the global health status, functional and symptoms scales (Table 8-19). Participants 1, 3 and 4 also presented either improved or similar scores post-intervention for the EORTC LC13, whereas participant 2 presented worse score for this scale (Table 8-19).

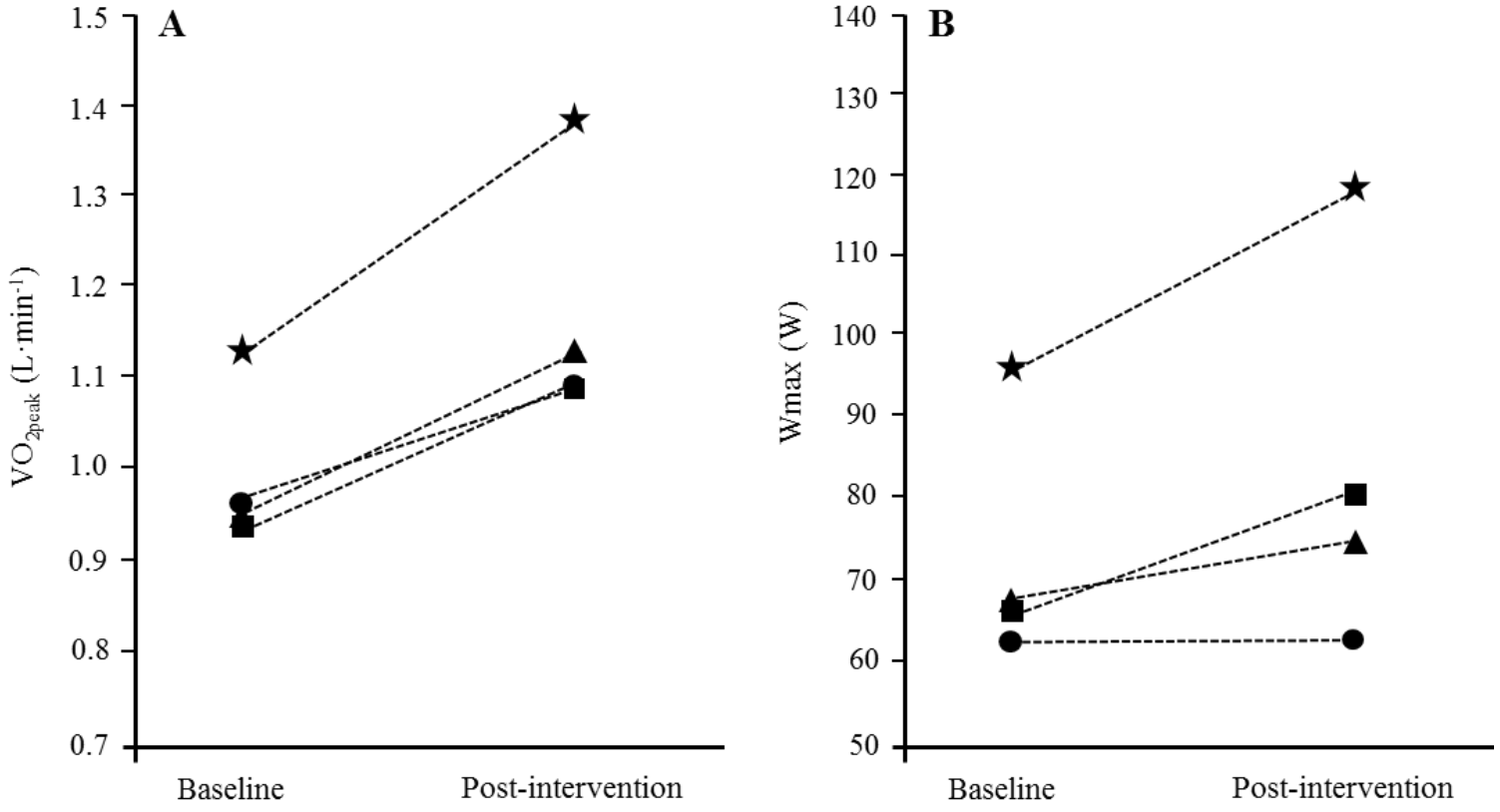

Figure 8-4: Baseline and post-intervention (A) VO_{2peak} (peak rate of oxygen consumption) and (B) Wmax (maximum work rate) data for participants 1 (▲), 2 (●), 3 (■) and 4 (✿) (exercise group).

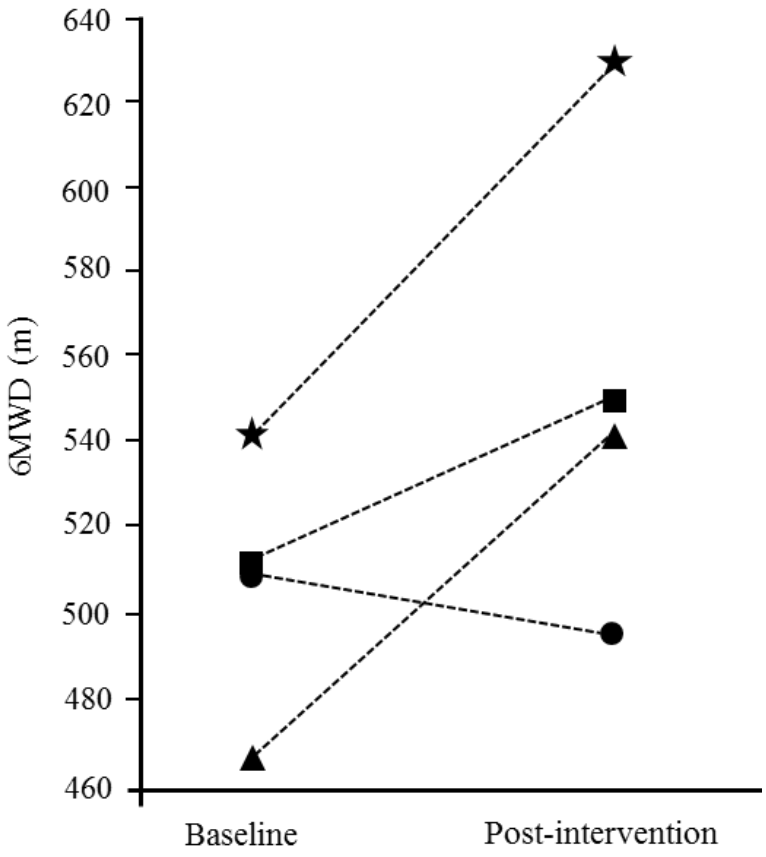

Figure 8-5: Baseline and post-intervention 6MWD (six-minute walk distance) data for participants 1 (▲), 2 (●), 3 (■) and 4 (★) (exercise group).

Table 8-18: Baseline and post-intervention exercise capacity results for participants 1, 2, 3 and 4 (exercise group)

Variable	Participant 1			Participant 2			Participant 3			Participant 4		
	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference
CPET												
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	11.1	13.6	2.5	15.4	16.3	0.9	16.7	18.9	2.2	16.1	18.5	2.4
VO_{2peak} (%pred)	50.3	60.8	10.5	81.1	90.7	9.6	87.8	101.2	13.4	51.0	65.0	14.0
Wmax (W)	68	74	6	62	62	0	67	79	12	96	119	23
Wmax (%pred)	49.8	55.0	5.2	83.9	85.7	1.8	115.3	135.9	20.6	53.2	64.0	10.8
BORGd on completion CPET	8	5	-3	9	6	-3	5	8	3	5	9	4
BORGf on completion CPET	8	7	-1	7	5	-2	4	6	2	6	10	4
Nadir SpO_2 (%)	93	90	-3	94	94	0	91	98	7	93	92	-1
HRmax (bpm)	112	108	-4	157	139	-22	122	119	-3	154	156	2
BR (%)	17	2	-15	21	36	15	11	34	23	37	32	-5
O_2 pulse ($ml \cdot beat^{-1}$)	8.4	10.4	2	6.1	7.7	1.6	7.7	9.1	1.5	7.4	9.7	2.3
AT (%VO_{2peak})	68	62	-6	52	63	11	69	74	5	52	63	11
VEmax/MVV (%)	83	98	15	79	64	-15	89	66	-23	63	68	5
6MWT												
6MWD (%pred)	79.2	91.1	11.9	96.6	96.5	-0.1	88.3	95.8	7.5	75.5	91.2	15.7
BORGd on completion 6MWT	7	4	-3	3	3	0	3	4	1	3	2	-1
BORGf on completion 6MWT	1	2	1	2	5	3	1	0.5	-0.5	5	3	-2
Nadir SpO_2 (%)	88	90	2	96	95	-1	96	96	0	92	93	1
Peak HR (bpm)	97	113	16	143	130	-13	126	120	-6	136	154	18

Abbreviations: 6MWD – Six-minute walk distance; 6MWT – Six-minute walk test; AT – Anaerobic threshold; BORGd – Dyspnoea; BORGf – Fatigue; BR – Breathing reserve; CI – Confidence interval; CPET – Cardiopulmonary exercise test; HR – Heart rate; HRmax – Maximal heart rate; O_2 pulse – Oxygen pulse; Pre – Baseline results; Post – Post-intervention results; SpO_2 - Arterial oxygen saturation measured via pulse oximetry; VEmax/MVV – Maximum minute ventilation, maximum voluntary ventilation ratio; VO_{2peak} – Peak rate of oxygen consumption; Wmax – Maximum work rate.

Table 8-19: Baseline and post-intervention HRQoL results for participants 1, 2, 3 and 4 (exercise group)

Variable	Participant 1			Participant 2			Participant 3			Participant 4		
	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference
SF-36												
PCS#	41	46	5	49	51	2	44	54	10	50	57	7
MCS#	60	65	5	63	65	2	56	60	4	61	62	1
Physical functioning#	55	70	15	55	75	20	65	90	25	80	100	20
Role physical#	56	75	19	100	100	0	56	88	33	88	100	12
Bodily pain#	62	80	18	84	61	-23	62	84	22	62	84	22
General health#	82	72	-10	80	100	20	67	87	20	97	97	0
Vitality#	56	81	25	88	88	0	69	88	19	75	94	19
Social functioning#	75	100	25	100	100	0	100	100	0	75	100	25
Role emotional#	100	100	0	100	100	0	75	100	25	100	100	0
Mental health#	90	100	10	90	100	10	80	90	10	100	100	0
FACT-L												
Physical well-being#	24	27	3	27	26	-1	24	28	4	24	28	4
Social/family well-being#	27	28	1	28	24	-4	24	24	0	28	28	0
Emotional well-being#	24	24	0	20	20	0	21	24	3	24	24	0
Functional well-being#	23	22	-1	24	28	4	19	27	8	23	28	5
Lung cancer subscale#	21	22	1	16	23	7	21	26	5	24	28	4
Total#	119	123	4	115	121	6	109	129	20	123	136	13
EORTC QLQ-C30												
Global health status#	67	83	17	100	100	0	58	83	25	50	100	50
Functional scales#	80	91	11	88	93	5	81	97	16	84	99	15
Symptoms scales†	21	12	-9	11	12	1	21	4	-17	19	4	-15
EORTC LC13†	7	6	-1	12	23	11	8	3	-5	37	11	-26

Abbreviations: EORTC QLQ-C30 – The European organization for research and treatment of cancer, quality of life questionnaire core 30 version 3; EORTC LC13 – Lung cancer subscale of the EORTC QLQ-C30; FACT-L – The functional assessment of cancer therapy – lung scale, version 4; MCS – Mental component score; PCS – Physical component score; Pre – Baseline results; Post – Post-intervention results; SF-36 – Medical outcomes study short form 36 general health survey.
#Greater scores reflect better outcome; †Lower scores reflect better outcome.

8.5.7.1.3 Peripheral muscle force

Isometric quadriceps torque and isometric handgrip force

Participant 4 did not attend Curtin University for the assessment of isometric quadriceps torque. Compared to the baseline value, the three participants who underwent isometric quadriceps torque assessment presented greater isometric quadriceps torque post-intervention (Table 8-20). Pertaining to isometric handgrip force, post-intervention, the values were either slightly higher or unchanged (Table 8-20).

8.5.7.1.4 Physical activity and sedentary behaviour

At baseline, participants 2, 3 and 4 wore the activity monitors for ≥ 10 hours/day for all 7 days, whereas participant 1 wore the monitors for ≥ 10 hours/day for 6 days. The average time that participants 1, 2, 3 and 4 wore the monitors was 15, 14, 13 and 13 hours/day, respectively. Post-intervention, all four participants wore the activity monitors for ≥ 10 hours/day for all 7 days. The average time that participants 1, 2, 3 and 4 wore the monitors was 14, 14, 13 and 13 hours/day, respectively. Changes in daily steps, sedentary behaviour, light intensity physical activity and moderate-to-vigorous intensity physical activity, from baseline to post-intervention, for each of the four participants, are presented in Figure 8-6.

Table 8-20: Baseline and post-intervention peripheral muscle force results for participants 1, 2, 3 and 4 (exercise group)

Variable	Participant 1			Participant 2			Participant 3			Participant 4		
	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference
Isometric quadriceps torque												
Torque (Nm)	118	146	28	101	112	11	97	108	11	-	-	-
Torque (%pred)	79	101	22	126	133	7	194	209	15	-	-	-
Isometric handgrip force												
Force (kg)	30	33	3	18	18	0	33	33	0	34	35	1
Force (%pred)	115	127	12	91	91	0	165	165	0	106	109	3

Abbreviations: Pre – Baseline results; Post – Post-intervention results.

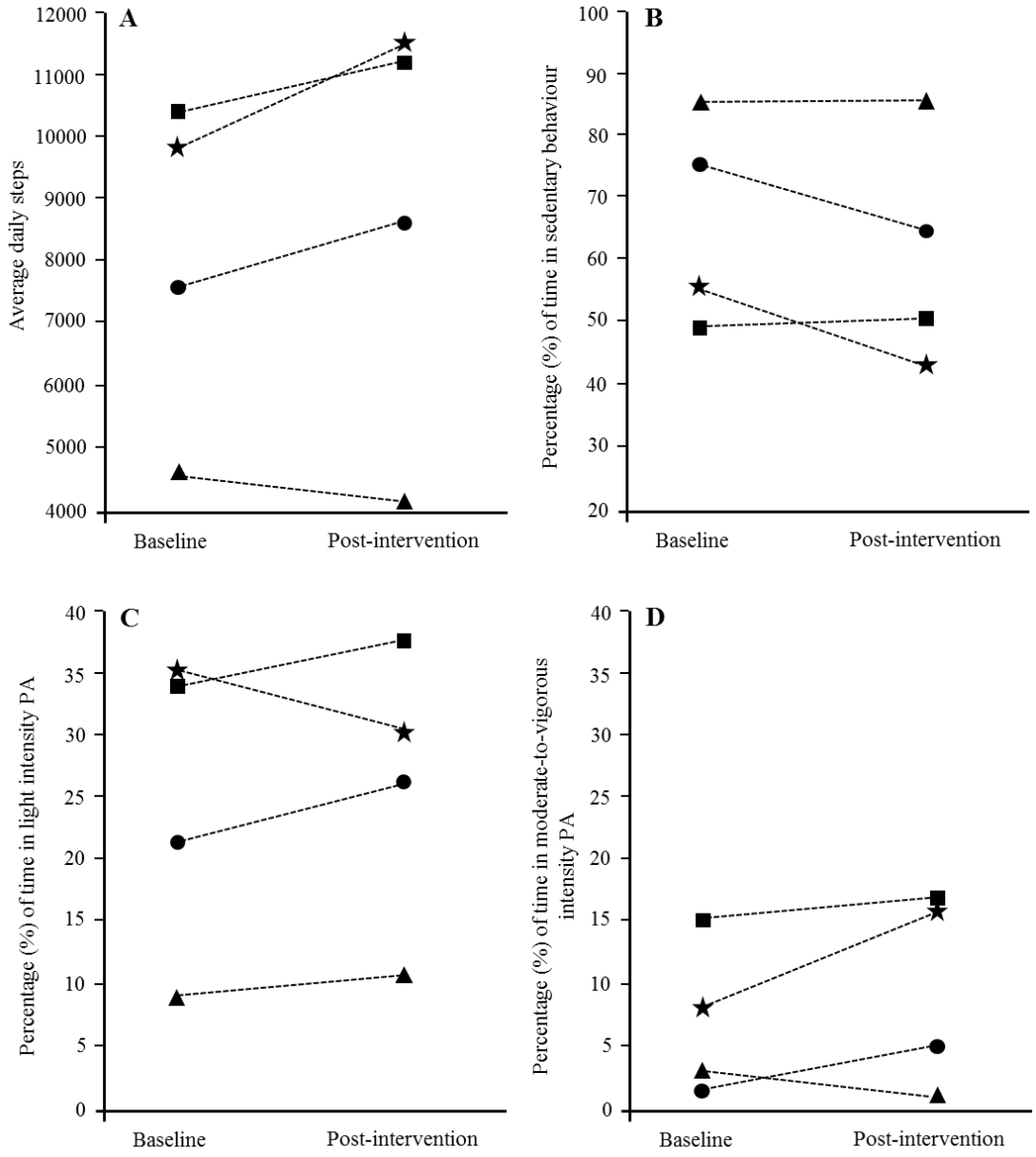

Figure 8-6: Baseline and post-intervention average daily steps (A); percentage of time in sedentary behaviour (B); percentage of time in light intensity physical activity (C) and; percentage of time in moderate-to-vigorous physical activity (D) data for participants 1 (▲), 2 (●), 3 (■) and 4 (✿) (exercise group).

Abbreviations: PA – Physical activity

8.5.7.2 Secondary outcomes

8.5.7.2.1 Lung function

Baseline to post-intervention variations in lung function ranged from -12% (D_LCO and MVV) to +1% (FEV_1) for participant 1; -12% (D_LCO) to +15% (MVV) for participant 2; +5% (D_LCO) to +43% (MVV) for participant 3 and; -4% (D_LCO) to +3% (MVV) for participant 4 (Table 8-21).

8.5.7.2.2 Functional limitation resulting from dyspnoea and fatigue

Changes on scores of the MMRC dyspnoea scale and FACIT-Fatigue collected at baseline and post-intervention in each of the four participants are presented in Table 8-22. Compared to baseline values, the MMRC dyspnoea score of participants 3 and 4 improved and the MMRC dyspnoea score of participants 1 and 2 remained unchanged. All the four participants presented improvement in their FACIT-Fatigue score.

8.5.7.2.3 Feelings of anxiety and depression

Anxiety and depression scores of the four participants either remained unchanged or improved (Table 8-22).

Table 8-21: Baseline and post-intervention lung function results for participants 1, 2, 3 and 4 (exercise group)

Variable	Participant 1			Participant 2			Participant 3			Participant 4		
	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference
FEV_1 (L)	1.25	1.26	0.01	1.37	1.46	0.09	1.54	1.69	0.15	1.58	1.58	0
FEV_1 (%pred)	50	50	0	84	92	8	88	97	9	48	48	0
FVC (L)	2.09	2.07	-0.02	1.68	1.77	0.09	1.97	2.18	0.21	3.09	3.16	0.07
FVC (%pred)	65	65	0	78	84	6	84	93	9	75	77	2
FEV_1/FVC (%)	60	61	1	82	82	0	78	78	0	51	50	-1
TLC (L)	3.25	3.11	-0.14	2.89	2.99	0.10	3.25	3.86	0.61	6.07	6.20	0.13
TLC (%pred)	67	64	-3	73	76	3	70	83	13	108	111	3
FRC (L)	1.93	1.83	-0.10	2.03	1.93	-0.10	1.93	2.57	0.64	3.78	4.18	0.40
FRC (%pred)	71	67	-4	92	87	-5	72	96	24	120	133	13
D_LCO ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	13.8	12.1	-1.7	10.8	9.3	-1.5	10.8	11.3	0.5	14.1	13.5	-0.6
D_LCO (%pred)	55	49	-6	57	50	-7	52	55	3	46	44	-2
MVV ($L \cdot min^{-1}$)	48	42	-6	54	62	8	44	63	19	70	72	2
MVV (%pred)	53	47	-6	76	88	12	58	84	30	65	67	2

Abbreviations: D_LCO – Single breath diffusing capacity for carbon monoxide; FEV_1 – Forced expiratory volume in one second; FRC – Functional residual capacity; FVC – Forced vital capacity; MVV – Maximum voluntary ventilation; Pre – Baseline results; Post – Post-intervention results; TLC – Total lung capacity.

Table 8-22: Baseline and post-intervention functional limitation resulting from dyspnoea, fatigue and anxiety and depression results for participants 1, 2, 3 and 4 (exercise group)

Variable	Participant 1			Participant 2			Participant 3			Participant 4		
	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference	Pre	Post	Difference
Dyspnoea												
MMRC†	1	1	0	1	1	0	1	0	-1	1	0	-1
Fatigue												
FACIT-Fatigue#	43	45	2	50	52	2	46	51	5	46	52	6
Anxiety and depression												
HADS – anxiety score†	3	2	-1	5	3	-2	4	4	0	0	0	0
HADS – depression score†	1	1	0	0	1	1	2	2	0	3	0	-3

Abbreviations: FACIT-Fatigue – Functional assessment of chronic illness therapy - fatigue subscale; HADS – The hospital anxiety and depression scale; MMRC – Modified medical research council dyspnoea scale; Pre – Baseline results; Post – Post-intervention results.
#Greater scores reflect better outcome; †Lower scores reflect better outcome.

8.6 Discussion

In people following curative intent treatment for NSCLC, an 8-week supervised exercise training programme that included aerobic and resistance exercises improved exercise capacity over and above any change seen in the CG. This finding corroborates the results of the Cochrane systematic review presented in Chapter 3 (105, 106). The within-group improvements in exercise capacity seen in the EG also corroborate findings of previous single-group studies (28, 29, 31). Regarding HRQoL, both the EG and CG demonstrated improvements in some subscales of the FACT-L, however no between-group differences were detected. This finding also corroborates the results of the Cochrane systematic review presented in Chapter 3 (105, 106) which showed no difference in HRQoL between exercise and control groups in people following lung resection for NSCLC. Finally, the 8-week supervised exercise training programme did not produce changes in peripheral muscle force, physical activity and sedentary behaviour, lung function, functional limitation resulting from dyspnoea, fatigue or feelings of anxiety and depression that were over and above any change seen in the CG.

Compared with previous studies in people following curative intent treatment for NSCLC, the current RCT has three novel aspects. First, this RCT investigated changes in maximal exercise capacity, measured using a laboratory-based test, of people following curative intent treatment for NSCLC. The three RCTs included in the Cochrane systematic review presented in Chapter 3 assessed exercise capacity using the 6MWT. The CPET provided novel information about improvement in VO_{2peak} and other variables of maximal exercise capacity. The between-group differences in VO_{2peak} may be promising as this outcome measure is a predictor of mortality in people with NSCLC (194). Second, one generic and two disease-specific HRQoL questionnaires were used, allowing for future comparisons with studies in NSCLC as well as in different populations. Third, this study included a broad range of outcomes measures, and as such is the first RCT to explore the effect of exercise training in people following curative intent treatment for NSCLC on physical activity and sedentary behaviour, functional limitation resulting from dyspnoea, fatigue and feelings of anxiety and depression.

8.6.1 Effects of the supervised exercise training programme

8.6.1.1 Exercise capacity

This is the first RCT of exercise training following curative intent treatment for NSCLC that investigated changes in maximal exercise capacity measured during a CPET. Importantly, this study demonstrated improvements in VO_{2peak} (both in %pred and in $L \cdot min^{-1}$) following exercise training that were greater than changes in VO_{2peak} seen in the CG. The between-group difference in VO_{2peak} (in %pred and $L \cdot min^{-1}$) on completion of the intervention period was demonstrated using ITT analyses, both with and without data imputation. Of note, all four participants of the EG group who completed at least 15 sessions (i.e. ≥ 60% of the total number of sessions) demonstrated an increase in VO_{2peak}. This may be particularly important given that VO_{2peak} has been shown to decrease after lobectomy for NSCLC (14, 40). A previous single-group study in 19 people following lung resection for NSCLC investigated changes in VO_{2peak} after a 14-week supervised exercise training programme (29). On completion of the intervention, both the VO_{2peak} in $L \cdot min^{-1}$ and the VO_{2peak} in $ml \cdot kg^{-1} \cdot min^{-1}$ increased (MD [95% CI] 0.10 [-0.01 to 0.19] $L \cdot min^{-1}$ and 1.1 [-0.3 to 2.5] $ml \cdot kg^{-1} \cdot min^{-1}$), however these changes were not significant ($p \geq 0.1$ for both). The authors were able to demonstrate that the inclusion of people receiving adjuvant chemotherapy during the exercise training period (8 of 19 participants) contributed to these non-significant findings (29). Specifically, when the analysis was restricted to the 11 participants who were not receiving adjuvant chemotherapy a significant increase was demonstrated in VO_{2peak}, expressed in $L \cdot min^{-1}$ and $ml \cdot kg^{-1} \cdot min^{-1}$ (MD [95% CI] 0.15 [0.05 to 0.24] $L \cdot min^{-1}$ and 1.7 [0.6 to 3] $ml \cdot kg^{-1} \cdot min^{-1}$; $p < 0.01$ for both) (29). The current RCT did not include people during adjuvant chemotherapy and the data showing an increase in VO_{2peak} support the results of the subgroup analysis from that previous single-group study (29).

In addition to increasing VO_{2peak} over and above any change seen in the CG, between-group comparisons also demonstrated that the EG improved O_2 pulse and AT during the CPET ($p < 0.05$ for both). This is the first study of exercise training in people following curative intent treatment for NSCLC to show such improvements. The O_2 pulse corresponds to the maximum oxygen consumption per heartbeat and it

is used as an estimator of stroke volume (72). The improvement demonstrated in O_2 pulse complements the finding of improved VO_{2peak} following exercise training. Improving O_2 pulse is a relevant finding as it has been demonstrated to be decreased at 3 months following lobectomy for NSCLC (14) and data from Chapter 5 (Table 5.2) demonstrated a difference between O_2 pulse of people following curative intent treatment for NSCLC (8 ± 3 ml·beat^{-1}) compared to healthy controls (11 ±4 ml·beat^{-1}) (p = 0.004). Regarding AT, findings from Chapter 5 (Table 5.2) demonstrated no difference in this variable between people following curative intent treatment for NSCLC and healthy controls. However, the improvement in AT following exercise training is a relevant finding that explains the mechanism by which maximal exercise capacity was improved. That is, exercise training is likely to have assisted in delaying the onset of blood lactate accumulation by enhancing the oxidative capacity of the exercising muscles (72).

Unlike two previous single-group studies that demonstrated improvements in Wmax after exercise training in people following curative intent treatment for NSCLC (29, 31), the current RCT did not show such improvement. Although the ITT analyses undertaken with (Table 8-14) and without data imputation (Table 8-8) demonstrated an increase in Wmax in the EG and a decrease in Wmax in the CG, neither the within-group nor the between-group changes were significant. This is likely to reflect a Type II error. Thus, had the current RCT recruited a greater number of participants, it is possible that the within and the between-group changes in Wmax would have reached statistical significance.

Regarding functional exercise capacity, the ITT analysis undertaken with and without data imputation showed that the EG increased 6MWD (MD [95% CI] 30 [2 to 58] m [ITT BOCF]; 45 [6 to 83] m [ITT without imputation]; $p < 0.05$ for both). The magnitude of this increase was greater than any seen in the CG (MD [95% CI] -7 [-30 to 17] m [ITT BOCF]; -8 [-36 to 20] m [ITT without imputation]; $p > 0.05$ for both). In people with NSCLC, the minimal clinically important difference (MCID) for the 6MWD has not been published. Nevertheless, the within and between-group MDs ranged between 30 and 52 m, being either similar to or exceeding the MCID for 6MWD in people with COPD (30 m (83) and 35 m (263)) and parenchymal lung disease (29 to 34 m) (78). Therefore, these MDs may be clinically important in

people following curative intent treatment for NSCLC. The improvements in 6MWD demonstrated in the current RCT corroborate the results of the Cochrane systematic review presented in Chapter 3 (105, 106) as well as findings from previous single-group studies (28, 29, 31). In people with NSCLC, an increase in 6MWD following exercise training is an important finding because this measure appears to be a valuable prognostic indicator in this population (264).

8.6.1.2 Health-related quality of life

This study demonstrated that, on completion of the intervention period, no within or between-group differences were observed in the components and domains of the SF-36 or in the scores of the EORTC QLQ-C30. Although the score of the lung cancer subscale of the FACT-L increased in the EG ($p = 0.04$) and the score of both social/family well-being and the lung cancer subscale of the FACT-L increased in the CG ($p < 0.05$ for both), no between-group differences were detected. These findings corroborate the results of the Cochrane systematic review presented in Chapter 3 (105, 106) that showed no difference in HRQoL between exercise and control groups in people following lung resection for NSCLC. Conversely, the lack of improvement in HRQoL seen in this RCT contrasts with earlier work in people with COPD (19, 23) and interstitial lung disease (20) in which improvements in HRQoL have been demonstrated following exercise training. However, compared to the results of studies in people with other cancers, the lack of improvement in HRQoL seen in this RCT is consistent with findings from a Cochrane systematic review in women with breast cancer (265). That is, Markes et al (265) demonstrated limited evidence for the effectiveness of exercise training to change HRQoL for women undergoing treatment for breast cancer. Although it is possible that exercise training is not effective at improving HRQoL in people with lung cancer, larger RCTs in this area are warranted.

8.6.1.3 Peripheral muscle force

This study demonstrated that, on completion of the intervention period, no within or between-group differences were observed in peripheral muscle force. This finding supports results reported in the previous RCT by Arbane et al (36) which investigated the effects of a 12-week home-based exercise training programme on

quadriceps force of people following lung resection for NSCLC. Quadriceps force was assessed via magnetic stimulation of the femoral nerve. The researchers demonstrated that, on completion of the intervention period, there was no between-group difference in quadriceps muscle force ($p > 0.05$). Unlike the RCT by Arbane et al (36) which reported quadriceps muscle force only in absolute values, the current study reported peripheral muscle force in absolute values and as a percentage of the predicted values. Of note, participants of the current study presented baseline isometric quadriceps torque that ranged from 97 to 103% of predicted values and isometric handgrip force ranging from 91 to 97% of predicted values. Therefore, the lack of within and between-group differences in peripheral muscle force may have been influenced by the fact that participants did not present with peripheral muscle weakness at the time of recruitment to current study. It can also be argued the resistance exercise component of the exercise training was ineffective. However, significant progression in the number of step ups and in biceps brachii muscle training from the first to the last session of exercise training was demonstrated (MD [95% CI] 35 [14 to 56] step ups; 21 [4 to 38] kg·sets·reps; $p < 0.05$ for both) (Table 8-7).

8.6.1.4 Physical activity and sedentary behaviour

On completion of the intervention period, no within or between-group differences were observed in physical activity or sedentary behaviour. This is the first study to investigate the effects of exercise training on physical activity and sedentary behaviour of people following curative intent treatment for NSCLC. Literature specific to the effects of exercise training on sedentary behaviour is somewhat scarce, however, the effects of exercise training on physical activity have been investigated in people with COPD (341, 358, 359). A systematic review and meta-analysis that included two randomised trials and five single group studies investigating changes in physical activity after exercise training in people with COPD demonstrated a significant yet rather modest effect size (0.12; $p = 0.01$) for change in physical activity (358). Authors of this systematic review were unable to locate any RCTs of exercise training for people with COPD that included measures of physical activity and therefore the results should be interpreted with caution.

The main strength of the physical activity and sedentary behaviour assessments in the current study was that two validated activity monitors were used. The SAM has been shown to be accurate in detecting step rate (compared to direct observation) regardless of walking speed or use of a walking aid (wheeled-walker) (235). The SAB is one of the most widely used physical activity monitors in the field of respiratory diseases and it has been shown to provide valid estimates of energy expenditure in people with chronic lung diseases as well as in other populations (229, 237-239). However, despite using validated monitors, the current study did not demonstrate improvements in physical activity or sedentary behaviour following exercise training. It is possible that with a larger sample size in the current RCT or with the inclusion of a behavioural approach as part of the intervention, the study would have been able to detect changes in physical activity and sedentary behaviour. A recent study that include people with COPD has suggested that only large samples ranging from 141 to 207 participants would afford the ability to detect changes in physical activity following exercise training (360). Further, it has been suggested that an approach comprising exercise training and a counseling programme aiming at behavioural changes would be needed in order to improve these outcomes (361).

8.6.1.5 Lung function

On completion of the intervention period, no within or between-group differences were observed in variables of lung function. This finding corroborates the findings of the Cochrane systematic review presented in Chapter 3 (105, 106) and from previous studies on exercise training for people following lung resection for NSCLC (101, 321) that demonstrated that the FEV_1 and FVC of people following lung resection for NSCLC do not change with exercise training. In addition to measures of spirometry (FEV_1 and FVC), the current study demonstrated no changes in total lung capacity, functional residual capacity, D_LCO and MVV on completion of intervention. Therefore, effectiveness of exercise training programmes in people following curative intent treatment for NSCLC should not be assessed using measures of lung function.

8.6.1.6 Functional limitation resulting from dyspnoea and fatigue

This study demonstrated that, on completion of the intervention period, no within or between-group differences were observed in functional limitation resulting from dyspnoea or fatigue. These findings are likely to be related to the fact that, at baseline, participants did not present with functional limitation resulting from dyspnoea or fatigue. Specifically, the median [interquartile range] MMRC dyspnoea score of the participants was 1 [1 to 2] with the majority of participants in both groups reporting MMRC dyspnoea scores of either 0 or 1. Regarding fatigue, the median [interquartile range] FACIT-Fatigue score of the participants was 42 [37 to 46]. This median is greater (i.e. better) than the mean FACIT-Fatigue score of 24 ± 13 reported in a group of 2,292 people with cancer and anemia (types of cancer not reported) and similar to the mean FACIT-Fatigue score of 44 ± 9 reported in a sample of general United States population (n = 1,010) (362). That is, at baseline participants of the current study did not present with symptoms of fatigue and hence, exercise training was unable to provide benefit in this outcome measure. No previous study has reported MMRC dyspnoea or FACIT-Fatigue scores in people following curative intent treatment for NSCLC and therefore comparison with other findings in NSCLC is not possible.

8.6.1.7 Feelings of anxiety and depression

This study demonstrated that, on completion of the intervention period, no within or between-group differences were observed in feelings of anxiety and depression. Similar to what was reported in Chapter 5 (heading 5.5.5.2 Feelings of anxiety and depression following curative intent treatment for NSCLC), this study showed that feelings of anxiety and depression were within normal ranges (HADS anxiety and depression scores ≤ 7) at baseline in both groups. Therefore, the lack of within and between-group differences in feelings of anxiety and depression may have been influenced by the fact that participants did not present feelings of anxiety and depression at the time of recruitment to the current study.

8.6.2 Limitations

It is clear that recruitment of participants to this study was challenging. Over a period of 26 months, 96 people following curative intent treatment for NSCLC were screened to participate in this study, of whom 71% (n = 68) were eligible and approached. Many of the eligible people following curative intent treatment for NSCLC did not consent due to difficulties with travelling to the hospital (if allocated for exercise training) or due to other demands on their time. Lack of interest, personal issues and a previously booked overseas vacation were other reasons for not consenting. The consent rate for the study was 26% (n = 18). Further, one participant was withdrawn by the investigators prior to randomisation as their cancer was upstaged to stage IIIB NSCLC. The final sample size was comprised of 17 participants.

As a consequence of the challenges in recruiting participants for this RCT, the final sample size was small, and it is acknowledged that this is the major limitation of the study. Another challenge and limitation was that only four of the nine participants in the EG were considered adherent to the exercise training programme. That is, only four of the nine participants in the EG completed at least 15 sessions (i.e. $\geq$ 60% of the total number of sessions) of exercise training. Three of the five participants who stopped training started feeling unwell for reasons not related to NSCLC. Of the remaining two, one stopped training due to being busy and the final participant was unwilling to travel to the hospital. These two limitations (i.e. small sample size and poor adherence) may have compromised the ability to detect within and between-group differences in several of the outcome measures. Notwithstanding these considerations, the data were able to demonstrate between-group differences in exercise capacity in people following curative intent treatment for NSCLC. Finally, this study includes a large number of between-group comparisons in a small sample, which increases the risk of a type I error. However, the significant between group differences in exercise capacity were demonstrated using two different methods of ITT analysis.

8.7 Conclusions

This study demonstrated that an 8-week supervised exercise training programme which included aerobic and resistance training increased maximal exercise capacity and 6MWD in people following curative intent treatment for NSCLC. No changes were observed in HRQoL, peripheral muscle force, physical activity and sedentary behaviour, lung function, functional limitation resulting from dyspnoea, fatigue and feelings of anxiety and depression. However, the ability to detect changes in outcomes other than exercise capacity might have been influenced by the small sample size and poor adherence to exercise training.

These findings support the findings of the Cochrane systematic review presented in Chapter 3. Further, they provide novel information showing that measures of maximal exercise capacity, such as VO_{2peak}, O_2 pulse and AT also improve following exercise training in this population. Taken together with the results presented in Chapter 5 demonstrating impairments in exercise capacity amongst people following curative intent treatment for NSCLC relative to healthy controls, these findings highlight the need to refer this population to exercise training programmes. Importantly, the novel finding of improvements in maximal exercise capacity measured during a CPET following exercise training may assist with changing the current practice patterns described in Chapter 4, which reported that referral to exercise training programmes following lung resection for lung cancer is still uncommon (248).

CHAPTER 9

SUMMARY AND CONCLUSIONS

The aims of this programme of research were to: (i) evaluate the current evidence for exercise training in people following lung resection for non-small cell lung cancer (NSCLC) and; (ii) examine current physiotherapy practice patterns for people undergoing lung resection for lung cancer in Australia and New Zealand. Further, in people following curative intent treatment (i.e. lobectomy with or without adjuvant chemotherapy) for stage I, II or IIIA NSCLC, this programme of research was designed to: (iii) evaluate the magnitude of impairments in functional outcomes; (iv) investigate patterns of sedentary behaviour and physical activity; (v) compare peak exercise responses as well as patterns of change in exercise responses during the six-minute walk test (6MWT) and the cardiopulmonary exercise test (CPET) and; (vi) investigate the effects of supervised exercise training on recovery of several outcomes.

This Chapter summarises the novel findings presented in this thesis and discusses the implications of these findings for clinical practice and future research.

9.1 Current evidence for exercise training in people following lung resection for NSCLC (Chapter 3)

This Cochrane systematic review comprised three randomised controlled trials (RCTs) of exercise training following lung resection for NSCLC and included a total of 178 participants. The meta-analyses demonstrated that exercise training increased exercise capacity, measured as six-minute walk distance (6MWD) (mean difference [MD] 50 m; 95% confidence interval [CI] 15 to 85 m), in people following lung resection for NSCLC. The minimal clinically important difference (MCID) for the 6MWD has not been published for this patient population. Nevertheless, a MD of 50

m exceeds the MCID for the 6MWD in people with chronic obstructive pulmonary disease (COPD) (30 m (83) and 35 m (263)) and parenchymal lung disease (29 to 34 m) (78) and, therefore, may be considered important in those following lung resection for NSCLC. An increase in 6MWD following exercise training is an important finding because this measure appears to be a valuable prognostic indicator for people with NSCLC (264).

This review suggests that exercise training has little effect on HRQoL for people following lung resection for NSCLC. This contrasts with earlier work in people with COPD (19, 23) and interstitial lung disease (20). Nonetheless, it is consistent with studies in people with other types of cancer (265). That is, Markes et al (265) demonstrated limited evidence for the effectiveness of exercise training to change HRQoL for women undergoing treatment for breast cancer. Larger RCTs using disease-specific HRQoL questionnaires are needed to further investigate the effects of exercise training on HRQoL in people following lung resection for NSCLC. Changes in lung function following exercise training were not demonstrated in this review and this is in agreement with the literature pertaining to the effect of exercise training on lung function for people with COPD (19).

Caution is needed when interpreting the findings of this systematic review as the quality of the evidence of the studies included in the analyses was rated as poor, mainly due to some risks of bias and small sample sizes. Although the quality of the evidence is low, the results of this review suggest that people following resection for NSCLC should be referred to exercise training programmes. This is especially true for those with impairments in exercise capacity.

9.2 Physiotherapy practice patterns for people undergoing lung resection (Chapter 4)

The results of this survey demonstrated that physiotherapy services for patients with lung cancer undergoing surgical resection throughout Australia and New Zealand currently focus on minimising the immediate risk of post-operative pulmonary complications. Although physiotherapy was most commonly commenced on the day following surgery, with walking-based exercise being the most frequently implemented treatment, referral to an exercise training programme was uncommon

for this patient population. This might have been due to a scarcity of well-designed studies that had been published prior to undertaking this survey demonstrating benefits of exercise training for this patient population. Prior to surgery, in 40% of the hospitals surveyed, patients were not assessed by a physiotherapist and the majority of respondents did not provide pre-operative exercise training for patients with lung cancer.

The response rate of 91% was greater than that achieved by previous surveys of physiotherapy for patients following thoracic surgery (response rate = 80%) (37), pulmonary rehabilitation (response rate = 83%) (268) and cancer care (response rate = 51%) (269). The high response rate suggests that the findings are unlikely to be influenced by a responder bias and thus provide a representative snapshot of current physiotherapy practice patterns for patients with lung cancer across Australia and New Zealand. Future comparisons are needed to objectively demonstrate any evolution in the management of lung cancer as the research in this field progresses.

9.3 Impairments in people following lobectomy for NSCLC compared to healthy controls (Chapters 5 and 6)

Compared to healthy controls, the greatest impairment detected in people following curative intent treatment for NSCLC was in exercise capacity. The magnitude of the decrement in measures of exercise was large and, in 71% of participants following curative intent treatment for NSCLC, their maximal exercise capacity (i.e. VO_{2peak}) was below the lower limit of normal (LLN). Also 45% of participants in the NSCLC group had a 6MWD below the LLN. These findings provide important information for clinicians working in the field. They highlight the need to refer people following curative intent treatment for NSCLC to exercise training programmes (especially those with a VO_{2peak} below the LLN). As reported in the Cochrane review presented in Chapter 3, in this patient population, exercise capacity improves with exercise training (105, 106). However, as demonstrated in the survey presented in Chapter 4, referral to exercise training programmes following lung resection for lung cancer is uncommon (248). Compared to healthy controls, people following curative intent treatment for NSCLC also demonstrated impairments in HRQoL, isometric handgrip force and the average number of steps taken each day. These findings emphasise that

future research is needed to identify strategies that can improve HRQoL, peripheral muscle force and physical activity in this population.

The proportion of waking hours spent in moderate-to-vigorous physical activity was similar between people following curative intent treatment for NSCLC and healthy controls. However, people following curative intent treatment for NSCLC performed less daily steps (8,863 ± 3,737 *versus* 11,856 ± 3,024 steps/day; $p = 0.009$), spent less time than healthy controls performing light intensity physical activity (20.7 ± 9.0% *versus* 26.4 ± 7.8% of waking hours, respectively; $p = 0.04$) and more time in prolonged uninterrupted bouts of sedentary behaviour (median [interquartile range] 49 [42 to 65] *versus* 42 [30 to 58]% of the total time in sedentary behaviour accumulated in bouts ≥ 30 min; $p = 0.048$). Prolonged time in sedentary behaviour is associated with an increase in waist circumference, higher concentration of triglycerides as well as a clustered metabolic risk score in the general population, and thus a potential risk factor for metabolic diseases (45-47). Of note, time spent in light intensity physical activity has been shown to be almost perfectly inversely related to time spent in sedentary behaviour (45). Therefore, strategies that aim to displace time spent in uninterrupted sedentary behaviour with light intensity physical activity may improve health outcomes in people following curative intent treatment for NSCLC. Embedding goal setting interventions (363) or psychosocial interventions (361) in exercise training programmes, aiming to decrease time is sedentary behaviour, is a promising area for future research and warrants further investigation.

This study was the first to include such a broad range of outcomes measures and compare them with age and gender-matched healthy controls. The novel findings are important for clinical practice as they will allow health professionals to provide people with NSCLC with realistic information regarding the impairments they may have following lung resection.

9.4 Comparison between peak and patterns of exercise responses following lobectomy for NSCLC during two exercise tests (Chapter 7)

This is the first study to compare peak exercise responses as well as patterns of change in HR and SpO_2 during the 6MWT with those elicited during the CPET in people following curative intent treatment for NSCLC. The findings of the study

suggest that the 6MWT elicits a somewhat lower peak HR than the CPET, however the magnitude of change from resting to peak HR (ΔHR) during the two tests was similar (MD [95% CI]; 7 [-15 to 1] bpm; $p = 0.10$). This was due to the slight non-significant difference in resting HR during the tests (resting HR 83 ± 10 [6MWT] *versus* 85 ± 13 [CPET]; $p = 0.35$). Further, the 6MWT elicited greater oxygen desaturation than the CPET in people following curative intent treatment for NSCLC. End-test symptoms of dyspnoea and leg fatigue were lower for the 6MWT and this might be related to the greater specific load borne by the quadriceps muscles during the CPET. In contrast with the CPET, patterns of change in HR and SpO_2 during the 6MWT were not linear. A plateau was observed in HR and SpO_2 responses during the 6MWT, demonstrating that this test should be considered a complementary test to the CPET. The 6MWD increased with test familiarisation (19 ± 19 m or 4 ± 4%; $p < 0.001$), and therefore clinicians should perform two tests to account for this effect when using the 6MWT to evaluate the effect of an intervention in people following curative intent treatment for NSCLC. The need for a third 6MWT was not assessed in the current study, however data from previous studies in people with COPD demonstrated no significant increase on a third 6MWT (96, 350).

Although in the current study ventilatory responses during the 6MWT were not measured, the comparable magnitude of ΔHR between the 6MWT and the CPET suggests that the 6MWT elicited a near maximum cardiac response and as such, the results of the 6MWT may be useful when prescribing the intensity of a walking training programme in people following curative intent treatment for NSCLC.

9.5 Effects of exercise training following lobectomy for NSCLC (Chapter 8)

This study demonstrated that an 8-week supervised exercise training programme resulted in improvements in exercise capacity in people following curative intent treatment for NSCLC. No changes in other outcome measures were observed. This finding corroborates results from the Cochrane systematic review presented in Chapter 3 (105, 106) and extends the findings of previous single-group studies by comparing the magnitude of change in the intervention group with those observed in a control group (28, 29, 31). Further, the study provided novel information showing

that measures of maximal exercise capacity, such as VO_{2peak}, O_2 pulse and anaerobic threshold as a percentage of the VO_{2peak} (AT) also improved following exercise training in this population.

To date, there has been no published study that investigated whether exercise training would be more beneficial to people following pneumonectomy compared to people following lobectomy for NSCLC. The impact of pneumonectomy on both lung function and exercise capacity is greater than the impact of lobectomy on the same outcomes (38, 40), and therefore, compared to lobectomy, it is likely that people following pneumonectomy would have greater benefits from an exercise training program. However, pneumonectomies are not performed as frequently as lobectomies and the feasibility of studies investigating the effects of exercise training for people following pneumonectomy versus people following lobectomy becomes compromised. The reason why pneumonectomies are not usually the surgical approach of choice is because both peri-operative and post-discharge mortality following pneumonectomy are three times as high as following lobectomy (364). The American College of Chest Physicians recommends that, for people with clinical stage I or II NSCLC, in whom a complete resection can be achieved, lobectomy or a sleeve or bronchoplastic resection is suggested over pneumonectomy (103).

The major limitation of the study was the small sample size, which was a consequence of the challenges in recruiting participants for this RCT. Another limitation was that only four of the nine participants in the exercise training group completed at least 15 exercise training sessions (i.e. 60% of the total number of sessions). These two factors may have limited the ability to detect within and between-group differences in several of the outcome measures. Notwithstanding these considerations, both ITT analyses (with and without data imputation) performed in this study did demonstrate important improvements in variables of maximal exercise capacity and 6MWD in people following curative intent treatment for NSCLC. In order to improve recruitment and adherence to exercise training, future studies should consider recruiting participants from multiple sites and offer flexibility of location to undertake exercise training. Taken together with the findings presented in Chapter 5, that demonstrated substantial impairments in exercise capacity relative to healthy controls, these findings provide an evidence base to

promote the referral of patients following curative intent treatment for NSCLC to existing exercise training programmes. Further research should investigate whether the improvements in variables of exercise capacity in people following curative intent treatment for NSCLC are maintained in the long term (i.e. 6 to 12 months following exercise training completion). Additionally, future studies should explore strategies to improve other outcomes such as HRQoL and time spent in light intensity physical activity and sedentary behaviour, that were demonstrated to be impaired in people following curative intent treatment for NSCLC (Chapter 5).

9.6 Summary and future directions

Chapter 3 of this thesis demonstrated that there is a scarcity of well-designed studies investigating the effects of exercise training in people following curative intent treatment for NSCLC. This scarcity may partially explain the findings from the survey presented in Chapter 4, that showed poor referral to exercise training programmes in this patient population at hospital discharge following surgery for NSCLC. Importantly, taken together, the impairments in several outcomes amongst people following curative intent treatment for NSCLC relative to healthy controls, demonstrated in Chapters 5 and 6, and the novel information showing that measures of maximal exercise capacity improve following exercise training, demonstrated in Chapter 8, highlight that existing pulmonary rehabilitation programmes should consider start enrolling this patient population as there is evidence of improvements in exercise capacity. Further, people who underwent curative intent treatment for NSCLC and present impairments in exercise capacity should be referred to exercise training programmes. Finally, Chapter 7 showed that the 6MWT can be an alternative exercise test to the CPET. Importantly, people following curative intent treatment for NSCLC who present with modest impairments in 6MWD may have considerable impairment in peak exercise capacity, and therefore may still benefit from participating in exercise training. Further, the results of the 6MWT may be useful when prescribing the intensity of a walking training programme in people following curative intent treatment for NSCLC.

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Appendix 1

Search strategy: MEDLINE (via PubMed)

#1 ((((lung cancer*[Title/Abstract]) OR non-small cell[Title/Abstract]) OR non small cell[Title/Abstract]) OR Lung Neoplasms[MeSH Terms]) OR Carcinoma, Non-Small-Cell Lung[MeSH Terms]

#2 (((((((((exercis*[Title/Abstract]) OR rehabilitat*[Title/Abstract]) OR aerobic*[Title/Abstract]) OR endurance[Title/Abstract]) OR strength*[Title/Abstract]) OR inspiratory muscle*[Title/Abstract]) OR respiratory muscle*[Title/Abstract]) OR treadmill[Title/Abstract]) OR walking[Title/Abstract]) OR cycl*[Title/Abstract]

#3 (training*[Title/Abstract]) OR program*[Title/Abstract]

#4 ((#1) AND #2) AND #3

Appendix 2

Search strategy: CENTRAL

#1 (lung cancer*):ti,ab,kw in Clinical Trials

#2 (non-small cell):ti,ab,kw in Clinical Trials

#3 (non small cell):ti,ab,kw in Clinical Trials

#4 MeSH descriptor Lung Neoplasms, this term only

#5 MeSH descriptor Carcinoma, Non-Small-Cell Lung, this term only

#6 (#1 OR #2 OR #3 OR #4 OR #5)

#7 (exercis*):ti,ab,kw in Clinical Trials

#8 (rehabilitat*):ti,ab,kw in Clinical Trials

#9 (aerobic*):ti,ab,kw in Clinical Trials

#10 (endurance):ti,ab,kw in Clinical Trials

#11 (strength*):ti,ab,kw in Clinical Trials

#12 (inspiratory muscle*):ti,ab,kw in Clinical Trials

#13 (respiratory muscle*):ti,ab,kw in Clinical Trials

#14 (treadmill):ti,ab,kw in Clinical Trials

#15 (walking):ti,ab,kw in Clinical Trials

#16 (cycl*):ti,ab,kw in Clinical Trials

#17 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)

#18 (training*):ti,ab,kw in Clinical Trials

#19 (program*):ti,ab,kw in Clinical Trials

#20 (#18 OR #19)

#21 (#6 AND #17 AND #20)

Appendix 3

Characteristics of excluded studies:

Adamsen 2012	
Reason for exclusion	Not post-operative patients
Andersen 2011	
Reason for exclusion	Not an RCT
Arbane 2009	
Reason for exclusion	Conference abstract of a included study
Arbane 2009a	
Reason for exclusion	Conference abstract of a included study
Barinow-Wojewodzki 2008	
Reason for exclusion	Not post-operative patients
Barinow-Wojewodzki 2008a	
Reason for exclusion	Not post-operative patients
Barton 2010	
Reason for exclusion	Not exercise training
Bradley 2011	
Reason for exclusion	Not post-operative patients
Cesario 2007	
Reason for exclusion	Not an RCT
Dimeo 2004	
Reason for exclusion	Mixed population. No access to specific data
Glattki 2012	
Reason for exclusion	Not an RCT
Granger 2011	
Reason for exclusion	Not an RCT
Hwang 2012	
Reason for exclusion	Mixed study. Few pre-operative participants

Jones 2008

Reason for exclusion	Not an RCT

Jones 2009

Reason for exclusion	Not an RCT

Jones 2010

Reason for exclusion	Not an RCT

Jones 2011

Reason for exclusion	Not an RCT

Kiziltas 2006

Reason for exclusion	Did not reply to several contact attempts

Licker 2011

Reason for exclusion	Not exercise training

Lin 2013

Reason for exclusion	Not exercise training

Lubbe 2001

Reason for exclusion	Not an RCT

Maddocks 2009

Reason for exclusion	Not post-operative patients

Nazarian 2004

Reason for exclusion	Not an RCT

Nici 2008

Reason for exclusion	Not an RCT

Oldervoll 2004

Reason for exclusion	Not an RCT

Parsons 2012

Reason for exclusion	Not exercise training

Peddle-McIntyre 2012

Reason for exclusion	Not an RCT

Peddle-McIntyre 2013

Reason for exclusion	Not an RCT

Riesenberg 2010

Reason for exclusion	Not an RCT

Shannon 2010

Reason for exclusion	Not an RCT

Shannon 2011

Reason for exclusion	Not an RCT

Spruit 2006

Reason for exclusion	Not an RCT

Weiner 1997

Reason for exclusion	Not post-operative patients

Woods 1999

Reason for exclusion	Not NSCLC

Appendix 4

MANAGEMENT OF LUNG CANCER PATIENTS QUESTIONNAIRE

SECTION 1: DEMOGRAPHIC INFORMATION

1) How long ago did you complete your initial qualification in physiotherapy? (tick one)

- ○ Less than 1 year
- ○ Between 1 and 5 years
- ○ Between 6 and 10 years
- ○ Greater than 10 years

2) Where did you complete your initial qualification in physiotherapy? (tick one)

- ○ New South Wales
- ○ Victoria
- ○ Australian Capital Territory
- ○ Queensland
- ○ South Australia
- ○ Western Australia
- ○ New Zealand
- ○ Other, please specify: _____

3) What is your highest tertiary qualification? (tick one)

- ○ Diploma
- ○ Bachelor's Degree
- ○ Master's Degree, please specify:
  _____
- ○ Doctorate, please specify:
  _____

4) How many years of experience in treating respiratory patients do you have? (tick one)

- ○ Less than 1 year
- ○ Between 1 and 5 years
- ○ Between 6 and 10 years
- ○ Greater than 10 years

5) **How many physiotherapists (fulltime equivalents [FTEs]) are employed in your hospital? (tick one)**
    - 1 to 5
    - 6 to 10
    - 11 to 20
    - 21 to 40
    - Greater than 40
    - Unsure

6) **Over the past month, approximately how many patients with lung cancer underwent *lobectomy* in your hospital? (tick one)**
    - Less than 4
    - 4 to 8
    - 9 to 12
    - More than 12
    - Unsure

7) **Over the past month, approximately how many patients with lung cancer underwent *pneumonectomy* in your hospital? (tick one)**
    - Less than 4
    - 4 to 8
    - 9 to 12
    - More than 12
    - Unsure

SECTION 2: PRE-OPERATIVE ASSESSMENT

8) Which <u>pre-operative assessments</u> does your hospital routinely use for patients scheduled to undergo surgical resection of lung cancer? Where necessary, please ask a member of the surgical team to assist you in your choices (e.g. lung function and exercise capacity) (tick all that apply)

<u>Lung Function</u>

- o Spirometry
- o D_LCO/T_LCO
- o V/Q scans
- o CT scans

<u>Exercise capacity</u>

- o Cardiopulmonary exercise test (Laboratory based test)
- o 6-Minute Walk Test (6MWT)
- o Stair Climbing Test
- o Incremental Shuttle Walk Test (ISWT)

<u>Other</u>

- o Muscle Strength (please specify muscles): _____
- o Maximal Respiratory Pressures
- o Health-related Quality of Life (please specify tool(s)): _____
- o Other tests, please specify: _____
- o Unsure

9) As a physiotherapist working with in-patients, are you involved in the pre-operative assessment of patients who will undergo surgical resection of lung cancer? (tick one)

- o Yes, I assess all of them
- o Yes, I assess most of them
- o Yes, I assess some of them
- o Yes, I assess a few of them
- o No, I never assess them

10) If you answered yes to the last question, please describe what assessments you do on patients who will undergo surgical resection of lung cancer?

_____

_____

_____

_____

_____

11) Do you provide pre-operative education to patients who will undergo surgical resection of lung cancer? (tick one)

- o Yes, for all of them
- o Yes, for most of them
- o Yes, for some of them
- o Yes, for a few of them
- o No, for none of them (proceed to question 13)

12) What proportion of patients who will undergo surgical resection of lung cancer are provided with information about the following topics by a physiotherapist, as part of their pre-operative education? Please choose one category for each possible education topics listed in the Table below.

	Proportion of patients				
Education topic	**0. None of them**	**1. A few of them**	**2. Some of them**	**3. Most of them**	**4. All of them**
A. Breathing techniques					
B. Cough/huff					
C. Explanation about the importance of upright positioning					
D. Explanation about the importance of early ambulation					
E. Shoulder exercises					
F. Thoracic exercises					
G. Explanation of post-operative physiotherapy sessions					
Other:					

13) Do your patients undergo a <u>supervised</u> exercise training programme <u>before</u> their surgery? (tick one)

- o Yes, all of them
- o Yes, most of them
- o Yes, some of them
- o Yes, few of them
- o No, none of them (proceed to section 3)

14) How do you decide which patients attend supervised exercise training <u>before</u> their surgery?

_____

15) As part of their pre-operative supervised exercise training programme, what proportion of patients prior to surgical resection of lung cancer, participate in the following types of exercises / techniques? Please choose one category for each possible exercise / technique listed in the Table below.

	Proportion of patients				
Exercises/techniques	**0. None of them**	**1. Few of them**	**2. Some of them**	**3. Most of them**	**4. All of them**
A. Breathing techniques					
B. Inspiratory muscle training					
C. Aerobic (walking)					
D. Aerobic (cycling)					
E. Strength (lower limbs)					
F. Strength (upper limbs)					
Other:					

16) What is the average duration of the exercise training programme before surgery?

- o Less than 1 week
- o 1 to 4 weeks
- o More than 4 weeks
- o Unsure

SECTION 3: POST-OPERATIVE MANAGEMENT

17) As a physiotherapist working with in-patients do you undertake early mobilisation of patients <u>following</u> surgical resection of lung cancer during their hospital stay? (tick one)

- Yes, for all of them
- Yes, for most of them
- Yes, for some of them
- Yes, for a few of them
- No, for none of them (proceed to question 20)

18) How soon do your patients with lung cancer commence physiotherapy treatment in wards <u>after</u> their surgery? (tick one)

- On the day of the operation
- Day one
- Day two
- Day three
- Day four
- Day five
- Day six or after

19) In what proportion of patients following surgical resection of lung cancer do you use the following types of exercises / techniques? Please choose one category for each possible exercise / technique listed in the Table below.

	Proportion of patients				
Exercises/techniques	**0. None of them**	**1. Few of them**	**2. Some of them**	**3. Most of them**	**4. All of them**
A. Breathing techniques					
B. Airway clearance techniques (other than cough/huff)					
C. Cough/huff					
D. Inspiratory muscle training					
E. Aerobic (walking)					
F. Aerobic (cycling)					
G. Strength (lower limbs)					
H. Strength (upper limbs)					
Other:					

20) After discharge, what proportion of these patients are referred to outpatient exercise training (pulmonary rehabilitation)? (tick one)

- ○ None of them (skip to question 21)
- ○ Less than 25%
- ○ 25 – 50%
- ○ 51 – 75%
- ○ More than 75%
- ○ Unsure

21) Who usually refers these patients following surgical resection to outpatient exercise training (pulmonary rehabilitation)? (please tick all that apply)

	Frequency			
Professional	**0. Never**	**1. Sometimes**	**2. Often**	**3. Always**
A. Physiotherapist				
B. Surgeon				
C. Physician				
D. Nurse				
Other, please specify:				

- o Unsure

22) Please indicate how much you think each of the following have influenced your management patients with lung cancer. Please choose one frequency category for each possible influence listed in the Table below.

	Frequency				
Influence	**0. Not at all**	**1. A little**	**2. Somewhat**	**3. A lot**	**4. Very much**
A. Published journal articles					
B. Text books					
C. Established practice in your hospital					
D. Personal experience					
E. Postgraduate education					
F. Professional development (workshops, seminars etc.)					
G. Initial academic education					
Other please specify:					

Thank you very much for completing this questionnaire. Your time is greatly appreciated.

If you are interested in the results of this survey, we will send you a summary of the findings once the study has been completed. Please provide your email address to allow us to forward this summary.

_____

Appendix 5

International Conference Presentations

2014:

European Respiratory Society – Annual Scientific Meeting (Munich, Germany): "Does the 6-minute walk test elicit maximal exercise responses in people following lobectomy for non-small cell lung cancer?"

European Respiratory Society – Annual Scientific Meeting (Munich, Germany): "Patterns of sedentary behaviour and physical activity following lung resection for non-small cell lung cancer"

National (Australian) Conference Presentations

2012:

Thoracic Society of Australia and New Zealand – Annual Scientific Meeting (Canberra, ACT): "Physiotherapy practice patterns for patients undergoing surgery for lung cancer – Preliminary results"

Cancer Council 4th Biennial Research Symposium (Perth, Western Australia): "Exercise capacity, physical activity and health-related quality of life after treatment for non-small cell lung cancer – Preliminary results"

2014:

Thoracic Society of Australia and New Zealand – Annual Scientific Meeting (Adelaide, South Australia): "Exercise training for people following lung resection for non-small cell lung cancer – A Cochrane Systematic Review"

Thoracic Society of Australia and New Zealand – Annual Scientific Meeting (Adelaide, South Australia): "Patterns of Sedentary Behaviour and Physical Activity Following Curative Intent Treatment for Non-Small Cell Lung Cancer"

Thoracic Society of Australia and New Zealand – Annual Scientific Meeting (Adelaide, South Australia): "Time Spent in Moderate-to-Vigorous Physical Activity

Following Lung Resection for Non-Small Cell Lung Cancer – A Comparison of Absolute and Relative Cut-Off Values"

Local Conference Presentations

2012:

Western Australia branch of the Thoracic Society of Australia and New Zealand – Annual Scientific Meeting (Perth, Western Australia): "Exercise capacity, physical activity and health-related quality of life after treatment for non-small cell lung cancer – Preliminary results"

Sir Charles Gairdner Hospital – Research Week (Perth, Western Australia): "Exercise capacity, physical activity and health-related quality of life after treatment for non-small cell lung cancer – Preliminary results

2013:

Cancer Council 8th State Cancer Conference (Perth, Western Australia): "Exercise training for people following lung resection for non-small cell lung cancer – A Cochrane Systematic Review

Appendix 6

Chapter 5: Correlation sub-analyses

Statistical analyses were performed using SPSS® (Statistical Package for Social Sciences, version 22.0 for Windows). The assumption of normality was assessed by graphical (frequency histograms and box plots) and statistical methods (Shapiro-Wilk test). Correlations between variables of people following lobectomy for NSCLC were calculated utilising Pearson's correlation coefficient.

Correlations (people following lobectomy for non-small cell lung cancer [NSCLC])

In people following lobectomy for NSCLC both VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) and Wmax during the CPET correlated with the 6MWD ($r = 0.6$ and $r = 0.45$, respectively; $p < 0.05$ for both).

1 Exercise capacity and health-related quality of life

Cardiopulmonary exercise test and SF-36

VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) was positively correlated with PCS ($r = 0.57$; $p = 0.009$) (Figure) as well as with four of the sub-components of the SF-36 (physical function, $r = 0.79$ (Figure); role physical, $r = 0.49$; vitality, $r = 0.68$; role emotion, $r = 0.45$; $p < 0.05$ for all). The BORGf on completion of the CPET was negatively correlated with PCS ($r = -0.45$; $p = 0.047$)

Six-minute walk test and SF-36

The 6MWD (% predicted) was positively correlated with three sub-components of the SF-36 (physical function, $r = 0.49$; role physical, $r = 0.47$; vitality, $r = 0.48$; $p < 0.05$ for all) but demonstrated only a trend for correlation with the PCS ($r = 0.39$; $p = 0.07$). The BORGf on completion of the 6MWT was negatively correlated with the sub-component social function ($r = -0.44$, $p = 0.04$).

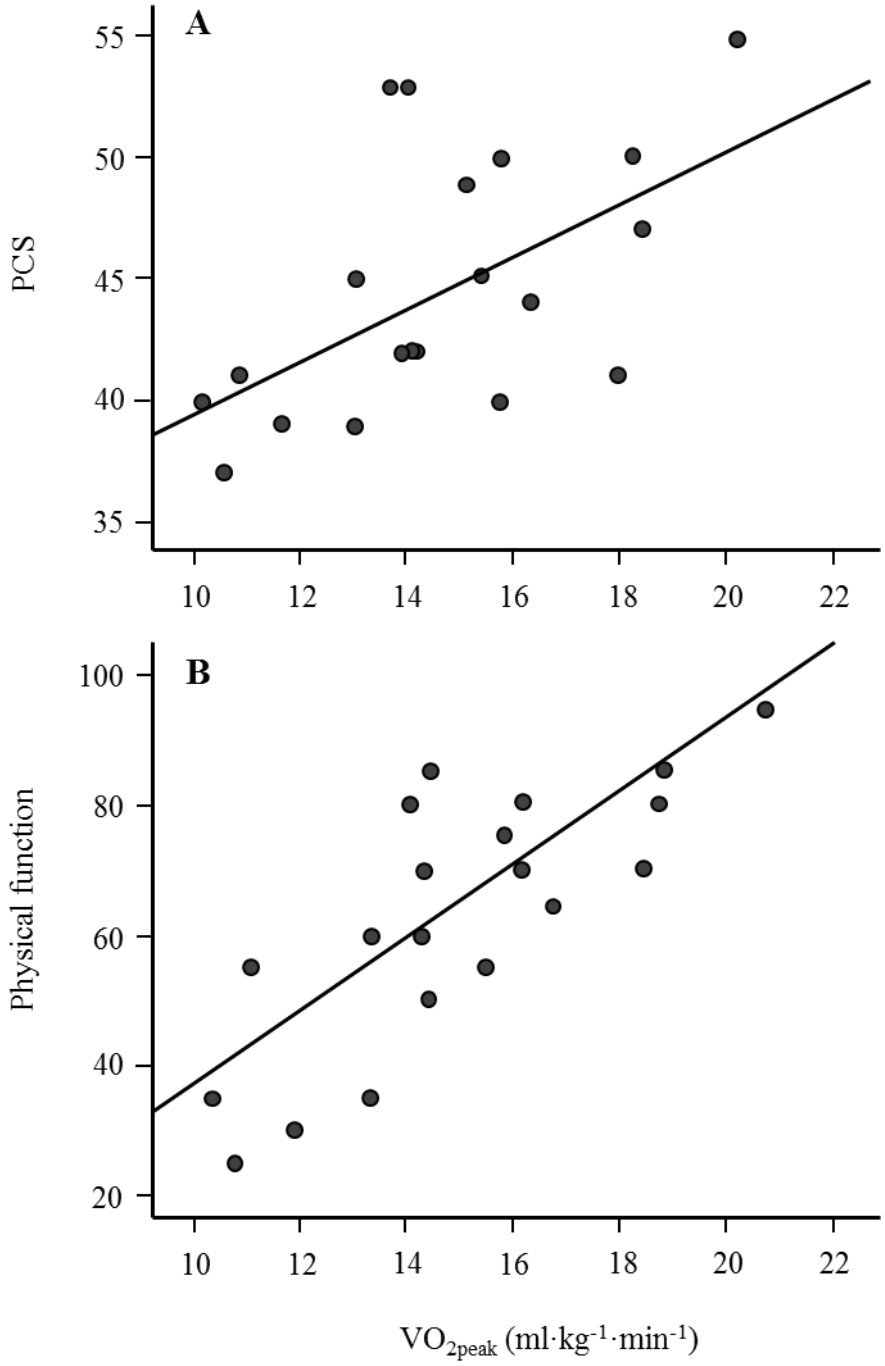

Figure 1: Scatter plots: correlation between maximal exercise capacity and HRQoL. Abbreviations: PCS – Physical component score; VO_{2peak} – peak rate of oxygen consumption. A) VO_{2peak} and PCS (r = 0.57; p = 0.009); B) VO_{2peak} and physical function (r = 0.79; $p < 0.001$)

2 Exercise capacity and isometric quadriceps and handgrip force

Positive correlations were found between VO_{2peak} ($L \cdot min^{-1}$) and both isometric quadriceps force (r = 0.74; p = 0.006) and handgrip force (r = 0.68; p = 0.001). Wmax was also correlated both isometric quadriceps and handgrip force (r = 0.71 and r = 0.69, respectively; $p < 0.02$ for both). No correlations between variables from the 6MWT and isometric quadriceps and handgrip force were detected.

3 Exercise capacity and physical activity

None of the variables from the CPET correlated with variables of physical activity. However, the 6MWD positively correlated with time spent in moderate-to-vigorous physical activity (r = 0.50; p = 0.03) and demonstrated a trend for correlation with daily steps (r = 0.41; p = 0.07).

4 Exercise capacity and lung function

Maximal exercise capacity correlated well with lung function (Table). Conversely, 6MWD, peak heart rate, nadir SpO_2 and symptoms during the 6MWT were not correlated with any of the variables of lung function.

5 Exercise capacity and feelings of anxiety and depression

No correlations have been found between variables of exercise capacity and the anxiety and depression domains of the HADS.

Table 1: Correlation (r values) between maximal exercise capacity and lung function

Variables	FEV_1 (L)	FEV_1 (% predicted)	FVC (L)	MVV ($L \cdot min^{-1}$)	MVV (% predicted)
Wmax (W)	0.56*	-	0.67*	0.58*	-
VO_{2peak} ($L \cdot min^{-1}$)	0.65*	-	0.55*	0.68*	-
VO_{2peak} (% predicted)	-	0.65*	-	-	0.49*
O_2 pulse ($ml \cdot beat^{-1}$)	0.60*	-	0.65*	0.61*	-

Abbreviations: BR – Breathing reserve; FEV_1 – Forced expired volume in 1 second; FVC – Forced vital capacity; MVV – Maximum voluntary ventilation; O_2 pulse – oxygen pulse; VO_{2peak} – Peak rate oxygen uptake;.Wmax – Maximum work rate. No values (-) means no significant correlation.

*$p < 0.05$

Appendix 7

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Chapter 3 has been presented in the following papers:

Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K.. Exercise training undertaken within 12 months following lung resection for patients with non-small cell lung cancer (Protocol). *Cochrane Database of Systematic Reviews.* 2012, Issue 7, Art No.: CD009955. DOI: 10.1002/14651858.CD009955.

Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K.. Exercise training for people following lung resection for non-small cell lung cancer – A Cochrane systematic review. *Cancer Treatment Reviews.* 2014; 40(4): 585-94.

Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K.. Exercise training undertaken by people within 12 months following lung resection for non-small cell lung cancer. *Cochrane Database of Systematic Reviews.* 2013, Issue 7, Art No.: CD009955. DOI: 10.1002/14651858.CD009955.pub2.

Chapter 4 has been presented in the following paper:

Cavalheri V, Jenkins S, Hill K. Physiotherapy practice patterns for patients undergoing surgery for lung cancer: A survey of hospitals in Australia and New Zealand. *Internal Medicine Journal.* 2013 Apr; 43(4):394-401.

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